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Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations

Morton Lippmann, Kazuhiko Ito, Arthur Nádas, and Richard T Burnett

Includes a Commentary by the Institute's Health Review Committee

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The Health Effects Institute, established in 1980, is an independent and unbiased source of information on the health effects of motor vehicle emissions. HEI supports research on all major pollutants, including regulated pollutants (such as carbon monoxide, ozone, nitrogen dioxide, and particulate matter) and unregulated pollutants (such as diesel engine exhaust, methanol, and aldehydes). To date, HEI has supported more than 200 projects at institutions in North America and Europe and has published over 100 research reports.

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HEI STATEMENT
Synopsis of Research Report 95

Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations

INTRODUCTION

Although evidence from epidemiologic studies supports an association between particulate matter (PM) and adverse health outcomes, many questions remain about how PM may cause such effects and who is affected. A major question is whether PM itself causes the effects, and if so, whether one of its components may be a better predictor of morbidity (illness) and mortality (death) than PM as a whole. Regulatory standards have focused on the size of PM particles and from 1971 to 1997 have moved to control successively smaller particles, from PM up to 40 μm in diameter (referred to as total suspended particles [TSP]) to less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$).

By definition, each of the larger PM indices contains elements of the smaller indices, so it is difficult to determine the relative effects of different PM metrics. Also, PM is a mixture of chemically and physically diverse dusts and droplets, and some of these components may be important to its health effects, such as hydrogen ions (H^+), which reflect particle acidity, and sulfate (SO_4^{2-}). Another complication is that gaseous pollutants are associated with similar health outcomes. Few epidemiologic studies have attempted to assess the relative effects of PM by size-fractionated metrics, or by its individual components, on illness and death.

APPROACH

Dr Morton Lippmann and colleagues at the New York University School of Medicine attempted to identify and characterize components of PM and other air pollution mixtures that were associated with excess daily deaths and elderly hospital admissions in and around the area of Detroit, Michigan. The study used publicly available data for 1985–1990 and 1992–1994, including measures of several different PM components as well as other air pollutants. Statistical models were used to weigh the strength of one pollutant or two pollutants concurrently. Models using three or more pollutants were not attempted owing to the difficulty of separating the effects of pollutants that rise and fall closely together, or are correlated. To better assess relationships between pollutants and health outcomes, the authors evaluated the extent to which (1) air pollutants tended to vary together in space and time, (2) results depended on the specific location where pollutants were sampled, and (3) results were influenced by multiple hospital admissions of some individuals in the study population during the study period. The main statistical method used was Poisson regression, with a generalized additive model to adjust for the effects of time trends, meteorologic differences, and other variables.

RESULTS AND INTERPRETATION

To evaluate whether human health was associated with outdoor levels of PM, the authors compared day-to-day fluctuations in air pollution with day-to-day fluctuations in deaths and hospital admissions in the Detroit area. If air pollution and adverse health outcomes are closely linked in time, then a daily average value of air pollution will be associated with a daily measure of health. This relationship is estimated in the current study by the relative risk, which is the relative increase in experiencing an adverse outcome (death or illness) given the presence of some risk factor (air pollutant), calculated for an increment in each air pollution variable equal to the difference between the 5th and 95th percentiles of their distributions.

For the period 1985–1990, the authors studied the risk of death due to TSP, PM_{10}, particles less than 40 μm and more than 10 μm in diameter (TSP–PM_{10}), sulfate from TSP (TSP–SO_4^{2-}), and several gaseous pollutants (sulfur dioxide, nitrogen dioxide, ozone, and carbon monoxide). The investigators reported that deaths from respiratory diseases were associated with PM_{10} and TSP. Ozone and nitrogen dioxide were also associated with all deaths together and with deaths due to circulatory causes. When the estimated

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI from June 1996 to September 1999 and conducted by Dr Morton Lippmann of the New York University School of Medicine, Tuxedo NY. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

effects of PM_{10} and one of the gaseous pollutants were determined concurrently, in a two-pollutant model, the association between PM_{10} and health outcomes remained the same, or became even stronger. This suggests that there was some effect of PM regardless of the presence of other pollutants. However, people are exposed to PM in a complex mixture of air pollutants, so assessing the results of a two-pollutant model (one PM metric and one gas) only begins to answer the question of whether PM is the cause of the observed effect.

For the period 1992–1994, the authors studied the risk of death and illness due to PM_{10}, $PM_{2.5}$, particles less than 10 μm and more than 2.5 μm in diameter ($PM_{10-2.5}$), H^+, and sulfate without sampling error (artifact-free sulfate, or SO_4^{2-}), and gaseous pollutants (sulfur dioxide, nitrogen dioxide, ozone, and carbon monoxide). Overall, the relative risks were about the same for all three of the PM mass indices evaluated (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$), and the PM mass indices were more significantly associated with health outcomes than H^+ or SO_4^{2-}. As the investigators pointed out, this result is inconsistent with their original hypothesis regarding the role of acidity in the air pollutant–mortality relationship.

The authors also highlighted their unanticipated findings for $PM_{10-2.5}$. Relative risks for $PM_{10-2.5}$ were similar to those for $PM_{2.5}$ and sometimes even higher—for example, with ischemic heart disease and stroke. However, the associations of elderly hospital admissions with $PM_{2.5}$ and $PM_{10-2.5}$ were significant for only a few one- or two-pollutant models; when $PM_{2.5}$ was evaluated with the gaseous pollutants in two-pollutant models, its estimated effect was often reduced. This was especially true when ozone was included in the model.

The authors also investigated the relationship between air pollutants and people geographically. Looking at a single pollutant across many sites, ozone, PM_{10}, and TSP tended to be at the same concentration level regardless of location within the general Detroit area. In an analysis of the TSP data for the time period 1981–1987, the investigators found no indication that the location where the air pollutant had been sampled influenced results.

This study compared the strength of association between different PM components and death and illness, but some features inherent to epidemiologic time-series studies complicate the comparison of estimated effects among air pollutants. Although the authors reported finding rates of death and illness associated with various pollutants, the data do not clearly support a greater effect of one pollutant over another, nor do they establish which pollutants are most likely to cause adverse health effects and which simply occur in a complex mixture with the causative pollutants. In general, determination of relative effect requires simultaneous consideration of multiple, relatively uncorrelated variables in a statistical model. Air pollutants exist in a mixture, have many common sources, and are therefore highly correlated, which makes it difficult to separate the effects of individual air pollutants.

The authors approached this question in analyses using size-fractionated PM metrics. Because $PM_{10-2.5}$ and $PM_{2.5}$ were not highly correlated in correlation coefficient and factor analyses, it is possible that the observed associations between coarse particles and health outcomes were not confounded by smaller particles. The finding of elevated and significant effects for $PM_{10-2.5}$ suggests that there may still be a rationale to consider the health effects of the coarse fraction as well as the fine fraction of PM.

Relatively few epidemiologic studies have evaluated the effect of $PM_{2.5}$ on human health. The current study could not definitively distinguish relative strengths of effect across the PM metrics, in terms of either particle size (TSP, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) or particle components (eg, H^+ or SO_4^{2-}), but the study does provide further general evidence that indicators of PM are associated with illness and death.

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Research Report 95

HEALTH EFFECTS INSTITUTE

Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations

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HEI STATEMENT

This Statement is a nontechnical summary of the Investigators' Report and the Health Review Committee's Commentary.

PREFACE

INVESTIGATORS' REPORT

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

Continued

COMMENTARY Health Review Committee

The Commentary about the Investigators' Report is prepared by the HEI Health Review Committee and staff. Its purpose is to place the study into a broader scientific context, to point out its strengths and limitations, and to discuss remaining uncertainties and implications of the findings for public health.

RELATED HEI PUBLICATIONS

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PREFACE

In 1994, HEI initiated a research program to investigate the complex issues associated with the health effects of exposure to particulate matter (PM)* in the air. This program was developed in response to growing concern about the potential public health significance of reported associations between daily fluctuations in levels of PM and changes in daily morbidity and mortality in time-series epidemiology studies. These results were questioned for a variety of reasons, including the lack of support from experimental studies and the lack of a mechanism to explain how such effects would occur. To address these issues HEI undertook two research initiatives in 1994: (1) the Particle Epidemiology Evaluation Project (Samet et al 1995, 1997), which evaluated six of the time-series epidemiology studies that had reported effects of PM on mortality; and (2) a program of toxicologic and epidemiologic studies (funded from RFA 94-2, "Particulate Air Pollution and Daily Mortality: Identification of Populations at Risk and Underlying Mechanisms"), which aimed to understand better how PM might cause toxicity and what factors might affect susceptibility. In all, HEI has issued five requests for research on PM and funded 34 studies or reanalyses over the last five years.

This Preface provides general regulatory and scientific background information relevant to studies funded from RFA 94-2 (or from the preliminary application process in the same time period), including the study by Morton Lippmann that is described in the accompanying Report and Commentary. All of the studies from RFA 94-2 have been completed and are either under review by HEI or have been published. The *HEI Program Summary: Research on Particulate Matter* (Health Effects Institute 1999) provides information on studies funded since 1996.

BACKGROUND

Particulate matter (PM) is the term used to define a complex mixture of anthropogenic and naturally occurring airborne particles. The size, chemical composition, and other physical and biological properties of PM depend on the sources of the particles and the changes the particles undergo in the atmosphere. In urban environments, these particles derive mainly from combustion, including mobile sources such as motor vehicles and stationary sources such as power plants. The most commonly used descriptor of particle size is *aerodynamic diameter*. Based on this parameter, ambient particles tend to fall into three size classes (often defined as *modes*): ultrafine or nuclei mode (particles less than 0.1 μm in diameter); fine or accumulation mode (particles between 0.1 and 2.5 μm in diameter), and coarse (particles larger than 2.5 μm in diameter). Fine and ultrafine particles are dominated by emissions from combustion processes while coarse particles are mostly generated by mechanical processes from a variety of noncombustion sources. Generally, the ultrafine and fine fractions are composed of carbonaceous material, metals, sulfate, nitrate and ammonium ions. The coarse fraction is composed mostly of mechanically generated particles and consists of insoluble minerals and biologic aerosols, with smaller contributions from primary and secondary aerosols and sea salts (US Environmental Protection Agency [EPA] 1996).

A number of early epidemiologic studies indicated that human exposure to high concentrations of PM, such as London fog, had deleterious effects (such as increased number of deaths), particularly in children, the elderly, and those with cardiopulmonary conditions (Firket 1931; Logan 1953; Ciocco and Thompson 1961; Gore and Shaddick 1968). Because of this apparent relation to increased mortality, the EPA has regulated the levels of ambient PM since 1971, when the Clean Air Act was first promulgated. This act authorized the EPA to set National Ambient Air Quality Standards (NAAQSs) for a number of potentially harmful air pollutants (including PM) in order to protect the health of the population, particularly those thought to be sensitive.

The first NAAQS for PM was based on controlling total suspended PM or particles up to 40 μm in diameter. In 1978, the standard was revised to regulate inhalable particles, or particles than can deposit in the respiratory tract and therefore have greater potential for causing adverse health effects. These are particles with an aerodynamic diameter of 10 μm or less (PM_{10}). More recent epidemiologic studies, published in the early 1990s, indicated a relatively consistent association between small short-term increases in PM levels and increases in both mortality and morbidity from respiratory and cardiovascular diseases (reviewed by the Committee of the Environmental and Occupational Health Assembly, American Thoracic Society [Bascom et al 1996]).

Some studies also suggested that long-term exposure to low levels of PM is associated with adverse effects (Dockery et al 1993; Pope et al 1995). These latter studies also

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

Table 1. Current NAAQSs for PM (set in 1997)

	PM_{10}	$PM_{2.5}$
Daily Standard	150 μg/m^3	65 μg/m^3
Annual Standard	50 μg/m^3	15 μg/m^3

pointed to a possible role of fine particles (less than 2.5 μm in aerodynamic diameter [$PM_{2.5}$]). In 1997, the EPA considered the evidence for the effects of fine particles sufficient to promulgate a fine particle standard while retaining the PM_{10} standard (US Environmental Protection Agency 1997) (see Table 1). The next review of the PM NAAQS is scheduled to be completed by the year 2002.

RESEARCH PROGRAM FROM HEI RFA 94-2

The wealth of epidemiologic data published in the early 1990s suggested an association between PM and health effects, but aspects of these fundings were not well understood. Problems involved uncertainties in the exposure estimates, confounding by weather or other factors, the role of copollutants, and the mechanisms by which particles may cause effects. Moreover, although epidemiologic findings were consistent across different communities exposed to distinct mixes and levels of pollutants, they were not well supported by either human chamber studies or animal inhalation studies aimed at delineating pathologic changes that might result in death. Failure of the experimental studies to provide support for the epidemiologic findings was attributed to insufficient statistical power, use of particles not representative of ambient particles, or use of animals not representative of the individuals susceptible to increased mortality.

By the mid 1990s, it became apparent that the research to advance our understanding of the association between exposure to particles and daily mortality found in the epidemiologic studies needed to focus on identifying (1) susceptible populations, (2) mechanisms by which particles may lead to increased mortality, and (3) characteristics of the particles responsible for the effects. It was recognized that both epidemiologic and experimental studies would be required.

The HEI program initiated in 1994 was aimed at addressing these research needs. Six epidemiologic and toxicologic studies were funded through RFA 94-2, and three additional studies were added through the preliminary application process. As a group, the five epidemiologic studies investigated: (1) social and medical factors that might increase the risk of mortality when particulate pollution increases (Mark Goldberg of the National Institute of Scientific Research, University of Quebec); (2) components of particulate pollution that might account for its effect on mortality (Morton Lippmann in the current report) and Erich Wichmann of the GSF Insitute of Epidemiology and Ludwig Maximilian University); and (3) cause of death (Harvey Checkoway of the University of Washington and Mark Goldberg) or possible pathophysiologic mechanisms that might lead to death in people exposed to particulate air pollution (Douglas Dockery of Harvard School of Public Health [see Dockery et al 1999]).

The four experimental studies tested the hypothesis that older animals or animals with preexisting lung or heart disease or respiratory infections are more sensitive to the acute effects of particles than healthy animals. They investigated possible mechanisms leading to mortality such as inflammation, changes in immune response, or changes in cardiac and respiratory function. Three of these studies used for the first time concentrated ambient particles (CAPs) (John Godleski of Harvard School of Public Health [see Godleski et al 2000], and Terry Gordon [see Gordon et al 2000] and Judith Zelikoff of New York University School of Medicine). In these CAPs studies, particles in the range of about 0.1 to 2.5 μm are concentrated while those greater than 2.5 μm are removed and those under 0.1 μm remain at the ambient concentration. CAPs exposures represent a significant fraction of ambient PM and provide a reasonable approach to mimicking the exposure to PM in epidemiology studies. The fourth experimental study (Günter Oberdörster of the University of Rochester School of Medicine and Dentistry [see Oberdörster et al 2000]) focused on evaluating the effects of different ultrafine particles that have been hypothesized to be more toxic than fine particles.

CONTINUING RESEARCH

Many of the key questions identified in the early 1990s are still relevant and much research is ongoing to address them. The research strategies have evolved, however, as results from previous studies have provided insights into which animal models and which endpoints may be the most helpful to evaluate. In addition, advances in exposure assessment and statistical methods have pointed to new approaches for conducting epidemiologic studies. Since RFA 94-2, HEI has funded a number of research projects that build on the new findings and approaches. These studies will be completed over the next two years (2000–2002).

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INVESTIGATORS' REPORT

Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations

Morton Lippmann, Kazuhiko Ito, Arthur Nádas, and Richard T Burnett

ABSTRACT

Indices of atmospheric particulate matter (PM)* have been reported to be associated with daily mortality and morbidity in a large number of recent time-series studies. However, the question remains as to which components of PM are responsible for the reported associations. Multiple PM components rarely are measured simultaneously. To investigate PM effects on mortality and morbidity, we used the multiple PM components measured in Windsor, Ontario, at a site only a few miles from downtown Detroit, Michigan. This study focused primarily on two study periods in which multiple PM components were measured in Windsor: 1985 to 1990, when levels of total suspended particles (TSP), sulfate from TSP (TSP–SO_4^{2-}), PM less than 10 μm in diameter (PM_{10}), and nonthoracic TSP (TSP–PM_{10}) were measured throughout the year; and 1992 to 1994, when data on PM_{10}, $PM_{2.5}$ (PM less than 2.5 μm in diameter), $PM_{10-2.5}$ (PM_{10} minus $PM_{2.5}$), particle acidity (H^+), and artifact-free sulfates (SO_4^{2-}) were available for mostly summer months. Mortality data were analyzed for the 1985 to 1990 study period, and data on both mortality and hospital admissions of elderly patients were analyzed for the 1992 through 1994 period. Poisson regressions were used to estimate the effects of these PM components and gaseous criteria pollutants on mortality (nonaccidental, circulatory, respiratory, and nonaccidental without circulatory and respiratory) and on hospital admissions of elderly patients (for pneumonia, chronic obstructive pulmonary disease [COPD], ischemic heart disease, dysrhythmias, heart failure, and stroke), adjusting for temperature and humidity, trends and seasonal cycles, and day of the week.

Both PM_{10} and TSP were associated significantly with respiratory mortality for the 1985 to 1990 period, with similar relative risk (RR) estimates for PM_{10} (RR = 1.123; 95% confidence interval [CI] 1.0361–1.218) and TSP (RR = 1.109; 95% CI 1.028–1.197), per 5th to 95th percentile increment. The effect-size estimates for TSP–SO_4^{2-} and TSP–PM_{10} were smaller and less significant. In two-pollutant models, simultaneous inclusion of gaseous pollutants with PM_{10} or TSP reduced PM coefficients by 0 to 34%. The effect-size estimates for total mortality, circulatory mortality, and total minus circulatory and respiratory mortality were less than those for respiratory mortality.

Ozone (O_3) and nitrogen dioxide (NO_2) also were associated significantly with total and circulatory mortality, but a simultaneous consideration of these pollutants with PM_{10} reduced PM_{10} coefficients only slightly, or even increased them. In these results, pollution coefficients often were positive at multiple lag days (0-day through 3-day lags were examined), but for PM indices, 1-day lag coefficients were most significant. However, when all combinations of multiple-day average exposures were examined, for cases in which multiple lag days were positive, the choice of single-day or multiple-day average exposure did not appreciably change the estimated effect sizes. An examination of temporal correlation showed that the order of spatial uniformity as expressed by the median site-to-site correlation was O_3 (0.83), PM_{10} (0.78), TSP (0.71), NO_2 (0.70), carbon monoxide (CO) (0.50), and sulfur dioxide (SO_2) (0.49), which suggests less exposure error for O_3 and PM_{10} than for the other measured pollutants. Thus, these results suggest that spatially homogeneous pollution indices show higher associations with measured health outcomes.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Investigators' Report is one part of Health Effects Institute Research Report 95, which also includes a Preface, a Commentary by the Health Review Committee, and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr Morton Lippmann, New York University School of Medicine, Department of Environmental Medicine, 57 Old Forge Road, Tuxedo NY 10987.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

In the 1992 to 1994 mortality data, all three of the PM mass indices (PM_{10}, $PM_{2.5}$, and $PM_{10–2.5}$) showed similar effect-size estimates and extent of significance for comparable distribution increments. By contrast, H^+ and SO_4^{2-} showed less significant associations with mortality. Among elderly patients admitted to hospitals, incidences of pneumonia and heart failure were associated with all the PM components. COPD and ischemic heart disease were associated most closely with the size-fractionated PM indices and O_3. The association of gaseous pollutants with these health outcomes was generally less than that for the size-fractionated PM indices. In two-pollutant models in which $PM_{2.5}$ and each of the gaseous pollutants were included, addition of gaseous pollutants, especially O_3, reduced the $PM_{2.5}$ coefficients. The magnitudes of the estimated relative risks for the PM mass indices (PM_{10}, $PM_{2.5}$, and $PM_{10–2.5}$) were approximately 1.05 per 5th to 95th percentile for mortality series; about 1.10 for COPD, ischemic heart disease, and heart failure admissions; and about 1.20 for pneumonia admissions.

Our results are not consistent generally with our study hypothesis that the relative particle metric effect size and strength of associations with mortality and morbidity outcomes, in descending magnitude, would be H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10}, and TSP. In general, the PM mass indices were associated more significantly with health outcomes than were H^+ or SO_4^{2-}. When both H^+ and SO_4^{2-} were significant, SO_4^{2-} was associated more strongly with the outcomes. These results suggest that PM components other than H^+ may be harmful, including the coarse component of PM_{10} (ie, $PM_{10–2.5}$).

INTRODUCTION

Associations between daily mortality and short-term changes in ambient air pollutants have been reported in the literature over many decades. Firket (1936) attributed 60 excess deaths to a severe smoke and fog (smog) episode in the Meuse Valley in Belgium in 1930 and estimated that if such a smog episode were to occur in London it could lead to over 3,000 excess deaths. In fact, the December 2 to 5, 1952, episode in London, in which peak black smoke (BS) levels exceeded 4,500 $\mu g/m^3$ and peak SO_2 reached 3,830 $\mu g/m^3$, was associated with 4,000 excess total deaths (US Environmental Protection Agency [EPA] 1982), of which 1,018 were ascribed to bronchitis (Ministry of Health 1954). The smoke control program stimulated by the December 1952 London smog episode required a shift from soft coal to coke, and BS levels began to decline dramatically in the late 1950s.

When a similar atmospheric inversion occurred in London in December 1962, the peak BS level was less than 60% of that in December 1952, but the peak SO_2 level was essentially the same. The excess mortality in December 1962 was about 700, and it was speculated that, because of the greater reduction in PM than SO_2, the PM, measured as BS, was more likely to cause excess mortality than SO_2. Black smoke, determined by light reflectance on a filter disc used to collect ambient air PM and converted by local calibration to gravimetric mass concentration, remained the standard metric for PM in the United Kingdom and much of Europe for many decades. As soot emissions were controlled, BS became an increasingly unreliable index of gravimetric mass concentration.

In the first major time-series analysis of daily London mortality for the winter of 1958 to 1959, Martin and Bradley (1960) and Lawther (1963) used the readily available BS and SO_2 data. They estimated that both pollutants were associated with excess daily mortality when their concentrations exceeded about 750 $\mu g/m^3$. Additional analyses of this data set led to different conclusions. For example, Ware and coworkers (1981) concluded that there was no demonstrable lower threshold for excess mortality down to the lowest range of observation (BS $\approx$ 150 $\mu g/m^3$).

Many analyses of the influence of air pollution on daily mortality in humans have taken advantage of the availability of a very large set of daily mortality data for greater London and temporally coincident data on temperature, humidity, BS, and SO_2. Daily data for winters became available in 1958, and year-round data became available in 1965. The environmental data were collected at seven sites in greater London, and most analyses of associations between the environmental variables and mortality have used the average values for these seven sites.

All of the time-series studies using these London data sets have found associations between daily mortality and temperature and, after adjustment (for temperature, day of the week, and season), have found residual associations of daily mortality with BS (Mazumdar et al 1982; Shumway et al 1983; Roth et al 1986; Schwartz and Marcus 1990). However, they differed in their conclusions about the extent of association of daily mortality with SO_2. In multiple regression analyses, Mazumdar and colleagues found no independent association of daily mortality with SO_2; Schwartz and Marcus found only a small role for SO_2; Shumway and associates found that SO_2 and BS were equally predictive; and Roth and coworkers concluded that it was not possible to separate the influence of BS and SO_2. We attribute these differences in results, in part, to the differences in the nature of the methods used to

account for the longer-wave phenomena in the time series that affect daily mortality (Thurston and Kinney 1995).

The acrid nature of the 1952 smoke episode led to speculation that the causal factor in the smog mixture might have been sulfuric acid (H_2SO_4), and anecdotal evidence (Dr DV Bates, personal communication, 1987) attributed improvements in the clinical status of hospitalized patients during the episode to the placement of ammonia air wicks in the crowded hospital wards. Commins and Waller (1963) developed a technique to measure H_2SO_4 in urban air, and between 1965 and 1972, they conducted daily measurements of aerosol strong acid (H^+) at a central London site (St Bartholomew's Medical School). On the basis of our initial time-series analysis of the data set, we had indicated that H^+ appeared to be associated more strongly with total daily mortality than either BS or SO_2 (Thurston et al 1989). However, a more detailed analysis of the same data set by Ito and associates (1993), involving pre-whitening, did not support our hypothesis that H^+ would have a greater degree of association with daily mortality than would BS or SO_2. In Ito and colleagues' (1993) analysis, temperature had the greatest influence in all seasons; all three of the pollution variables (same day and lagged one or two days) were significantly associated with daily mortality, and it was not possible to assign a dominant role to any one of them because the temporal fluctuations of the pollutants were highly collinear. A further analysis of the central London data set confirmed that these pollution effects could be separated from that of temperature (Lippmann and Ito 1995).

Thus, the analysis of past London data, although it generally suggested PM effects, did not provide conclusive evidence as to the specific component of PM that may have been responsible for the observed increase in daily mortality. Since then, the focus of observational epidemiologic investigation of acidic aerosols has shifted from London to US and Canadian cities. In contrast to the winter-type, combustion-derived primary-acid aerosols in historic London, H^+ aerosols in the northeastern United States and Canada are largely secondary products derived from SO_2 via oxidation facilitated by products of photochemical reactions; they are most prevalent during summer.

A series of hospital admissions studies conducted in Canada and the US (Bates and Sizto 1983, 1987; Thurston et al 1992, 1994; Burnett et al 1994, 1997a,c; Delfino et al 1994; Gwynn et al 1999) evaluated the effects of summer haze air pollution. These all examined similar major respiratory categories (eg, acute bronchitis and bronchiolitis, pneumonia, COPD, asthma). Initial findings by Bates and Sizto (1983, 1987) suggested general effects of summer haze as indicated by SO_4^{2-} and O_3 associations with respiratory categories of hospital admissions. The other studies therefore sought to identify those components of summer haze (SO_4^{2-}, H^+, and O_3) responsible for the observed associations in the same outcomes. These studies focused primarily on the summer months, and most reported associations between the summer haze components (SO_4^{2-}, O_3, and H^+), as well as other PM indices, and hospital admissions for respiratory difficulties.

Only a small number of mortality time-series studies have examined multiple PM components. The data from the Harvard Six Cities Study were analyzed by Schwartz and coworkers (1996). Their main hypothesis was that fine particles, but not coarse particles, were specifically associated with daily mortality, and their results were generally supportive of the hypothesis. They also reported that although SO_4^{2-} mass was associated significantly (but less strongly than was $PM_{2.5}$) with mortality, H^+ was not. However, it should be noted that the sample size available for H^+ in this study, as well as in an earlier study by Dockery and coworkers (1993), was much smaller (13% to 30%) than the sample size for $PM_{2.5}$, which may have contributed to the observed lack of association.

Thus, although a large number of studies reported associations between one of the PM indices and daily mortality or hospital admissions, there have been only a few studies in which multiple PM indices, for either size fraction or chemical constituents, were available. Our study took advantage of the rich source of data collected at a Canadian site in Windsor, a few miles from downtown Detroit, and combined them with US air pollution data to study the association of PM components with mortality and morbidity in the Detroit metropolitan area.

SPECIFIC AIMS

Our primary objective was to use available data on daily mortality, hospital admissions for total, respiratory and cardiovascular diseases, and ambient concentrations of air pollutants to identify and characterize the conditions of pollutant exposure that were associated most closely with excess daily mortality and hospital admissions. We hypothesized that the closest associations would be attributable to airborne PM, and more specifically to particles deposited in the airways of the tracheobronchial region (PM_{10}) and/or to fine particles ($PM_{2.5}$), and especially to the SO_4^{2-} and aerosol H^+ components of $PM_{2.5}$.

Additionally, our aim was to investigate the issues that are important in the interpretation of time-series analysis of multiple air pollutants. These are the relative spatial

variability of air pollutants; the effects of the choice of monitoring sites; and the influence of multiple admissions in the estimated pollution risks.

METHODS

DATA

Air Pollution Data

We had two sources of (nonoverlapping) air pollution data: the EPA's Aerometric Information Retrieval System (AIRS) database and Canadian air pollution data available from Environment Canada. In addition to the data available for a large number of air monitoring stations in Detroit from the AIRS database (see Table 1), data including PM_{10}, $PM_{2.5}$, TSP, SO_4^{2-}, and H^+ aerosol measurements were available from two air monitoring stations located in the US-Canada border city of Windsor, Ontario (see Figure 1). This provided a unique opportunity to study the interrelations among various PM components and their potential impact on human health.

Windsor Air Pollution Data The data from Windsor were provided by Drs Rick Burnett (Health Canada) and Jeff Brook (Environment Canada). The files contained data from two stations in Windsor, one on University Avenue and another at the intersection of College and Park streets. The variables included size-fractionated mass: fine ($PM_{2.5}$); PM_{10}; coarse ($PM_{10-2.5}$); SO_4^{2-}; and H^+. Extensive data for these variables (490 days for the size-fractionated PM data and 344 days for SO_4^{2-} and H^+ data) were available from the College/Park road site for 1992, 1993, and 1994. Data were collected every day May through September, and every sixth day October through April during the 3-year period. Daily TSP and its SO_4^{2-} also were available for 1981 to 1990 from the University Avenue site.

Details of the measurement methods used at the Windsor site are described in Brook and coworkers (1997a,b). Briefly, the fine-particle samples for chemical analysis were collected using an annular denuder system (Koutrakis et al 1988), which consisted of a size-selective inlet (a 2.5-µm Teflon-coated aluminum cyclone), denuders to remove gases, and filter packs (with preweighed 37-mm Teflon filters). The flow rate for the denuders was 10 L/min. The H^+ concentrations were determined from pH measurements, and SO_4^{2-} concentrations were determined by ion chromatography. The $PM_{2.5}$ and PM_{10} masses were determined from preweighed 37-mm Teflon filters using dichotomous samplers with a total flow rate of about 16.7 L/min. The 24-hour sampling started at approximately 8 AM EST for both samplers. Further details of the analytical methods can be found in Brook and associates (1997a,b) and in EPA (1992).

AIRS Data Because a relatively large volume of air pollution data, with varying frequency, length, and collection periods for multiple pollutants, was available, we first examined the collection period and the extent of missing data for all the air monitoring sites to assess their usefulness in data analyses. To cover the period for which the Windsor measurements were available, we retrieved data for the years 1981 through 1994. Using our log-in account for the AIRS database, we first retrieved the AIRS work file in the AMP310 format, which describes distribution characteristics (eg, means, percentiles, maximum, etc) for each year, as well as observation counts and site descriptions. We retrieved the data for TSP, PM_{10}, SO_2, NO_2, O_3, and CO for Wayne County from 1981 through 1994. The resulting work files were transferred over the Internet to the Nelson Institute at New York University.

The AIRS work files contained information on the measurement methods used for each of the air pollutants. Both TSP and PM_{10} were measured using high-volume samplers. SO_2 was measured using several different methods during the study period (ie, colorimetric, ultraviolet fluorescence, and pulsed fluorescence), but the reported minimum detection limits for these methods were comparable (ie, ~2 ppb for hourly values). NO_2 was measured using chemiluminescence or ultraviolet methods (the reported minimum detection limits were essentially the same). CO was measured using nondispersive infrared methods.

A large number of stations collected data for extended periods; however, some collected data intermittently, or for only a short period of time. In order to conduct data analyses with a sufficient number of observations, we eliminated stations with less than two years of the scheduled sampling frequencies. The decision was based on the fact that, to our knowledge and in a review of the literature, no time-series study that reported significant associations of PM with mortality used fewer than 120 daily average observations.

We subsequently obtained raw data in AIRS work-file format AMP355. This format provides daily average values for PM indices and hourly observations for gaseous pollutants. For gaseous pollutants, only 1-hour average values were retrieved (3-hour, 8-hour, and 24-hour averages were available for some of the pollutants). The work files were transferred to our computer and processed to compute daily 24-hour averages for gaseous pollutants. We searched for any change in units (eg, $\mu g/m^3$ to ppm or ppb) over the

Table 1. AIRS Monitoring Sites Available in Wayne County, Michigan, for 1981 through 1994

Site ID	Map Label	PM_{10}	TSP	SO_2	O_3	CO	NO_2	Land Use	Location Setting
261630001	a	•	•	•	•	•		COM	SUB
261630002	b	•	•	•				IND	SUB
261630003	c		•	•				COM	SUB
261630005	d	•	•	•				IND	SUB
261630009	e		•	•				RES	SUB
261630014	f		•	•		•		RES	SUB
261630015	g	•	•	•				COM	URB
261630016	h		•	•	•	•	•	RES	URB
261630017	i		•	•				RES	SUB
261630018	j		•	•				COM	SUB
261630019	k		•	•	•		•	RES	SUB
261630020	l		•	•			•	COM	URB
261630021	m					•		COM	URB
261630023	n		•	•				IND	URB
261630025	o	•		•		•		COM	SUB
261630027	p			•		•		IND	URB
261630029	q		•	•		•	•	COM	URB
261630033	r	•	•	•				IND	SUB
261630062	s			•		•		RES	URB
261630083	t					•		MOB	URB
261630092	u		•	•				RES	URB
261632002	v	•	•	•	•	•		RES	SUB
261632003	w		•	•				COM	SUB
261639001	x		•					COM	SUB

•: at least 2 years of data available during 1981 through 1994; sites with less than these criteria for any of the pollutants are not listed. COM: Commercial; IND: Industrial; RES: Residential; MOB: Mobile; SUB: Suburban; URB: Urban.

years, and necessary conversions were made to ensure unit consistency.

When we eliminated the monitoring sites with less than two years of data, we were left with 24 sites with varying amounts of data for each of the six pollutants. Table 1 shows the availability of air pollution measurements for these 24 AIRS sites. SO_2 was measured by the largest number of monitoring sites (21), followed by TSP (19). The AIRS site identification, land use, and location setting, as described in the AMP310 files, are also listed in Table 1. The reference label (alphabetical) for each site is listed as well. It should be noted that there were two sites (b and r) that measured PM_{10} daily, rather than on every sixth day. The land use description for these two sites is industrial, suggesting that the daily monitoring of air quality reflects the proximity of industries. The locations of these two sites are essentially identical, and it appears that site r replaced site b in the middle of 1990. PM_{10} data from AIRS became available mid 1985.

The locations of these sites, as well as population densities by zip code, are shown in Figure 1. The air monitoring sites are reasonably distributed throughout the county in relation to population distribution, but several sites are within a few miles of each other. The Windsor sites (y and z) are located within a few miles of the clusters of Detroit sites. Thus, there is no reason to treat the Windsor sites any differently from the Detroit sites on the basis of their locations. It is also possible to compare the Detroit sites PM_{10} and TSP data with those of the Windsor sites. Seven sites, including Windsor site y, had periods in which both TSP and PM_{10} were collected. The 5 years (1985–1990) covered by these data in Detroit allowed extensive examination of relations among various PM components.

One of the Windsor sites (Canadian ID 060204) was located at University Avenue, and the other (ID 060211) was located at the corner of College and Park streets. These sites were labeled as y and z, respectively.

Weather Data

The weather data for Detroit Metropolitan Airport (Weather Bureau, Air Force, and Navy [WBAN] ID: 94847) were extracted from a compact disk (EarthInfo, Boulder

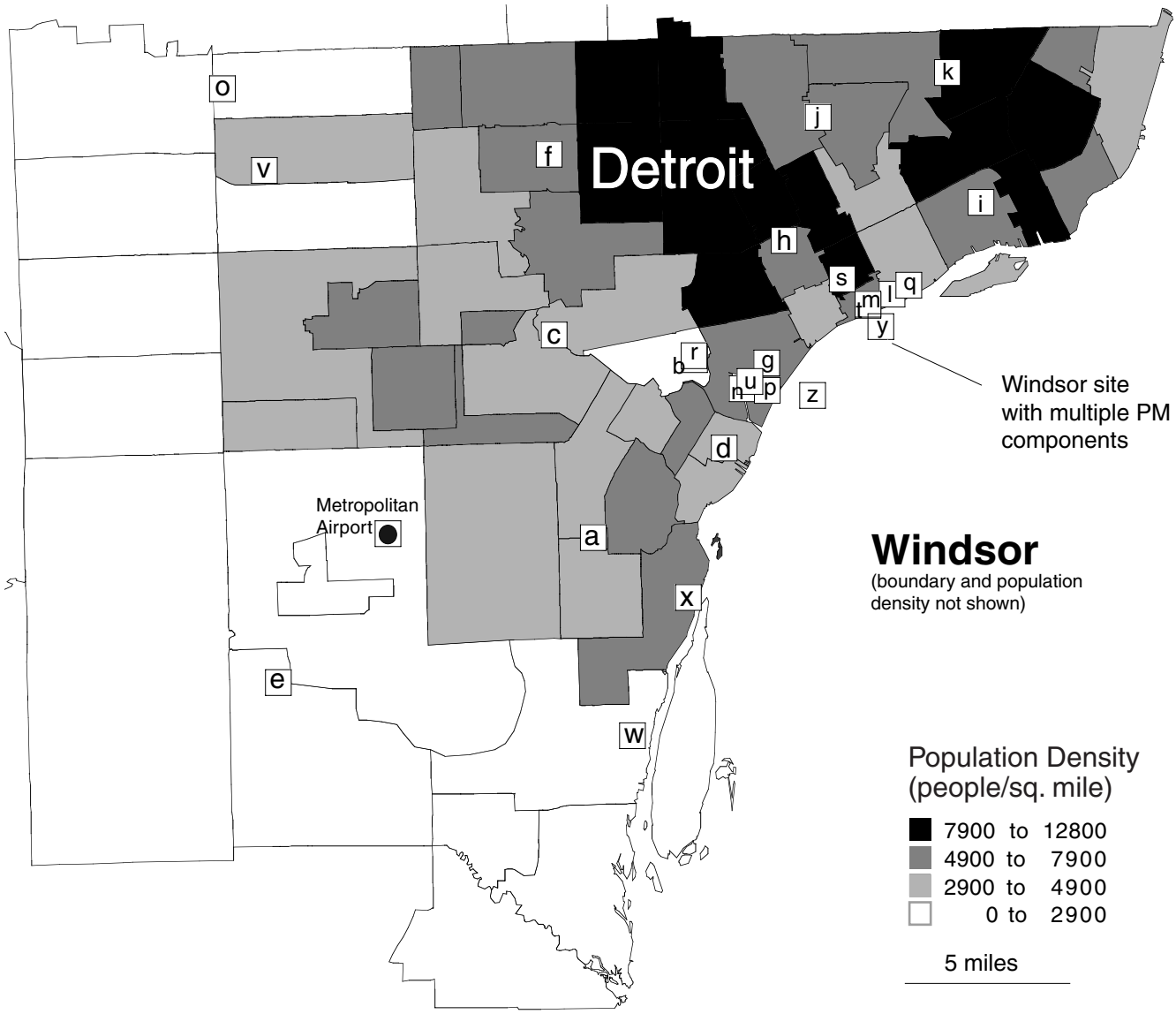

Figure 1. Wayne County MI Population Density by zip-code (1990 Census) and the location of air monitoring stations (see Table 1 for labels).

CO), which compiled the surface airways database of the National Climatic Data Center (NCDC). Daily average temperature and relative humidity data were retrieved.

Health Outcomes

A comparison of the availability of AIRS and Canadian data resulted in two main study periods for which various PM components could be examined in time-series analyses: 1985 to 1990, Wayne County, PM_{10}, TSP, and TSP–SO_4^{2-}; and 1992 through 1994, Wayne County, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4^{2-}, and H^+. The 1992 through 1994 study period was our primary interest because of the greater variety of data on PM size and chemical components. Therefore, data on both mortality and hospital admissions of elderly patients were analyzed for 1992, 1993, and 1994. Only mortality records were analyzed for the 1985 to 1990 period. For these two main periods studied, mortality and hospital admission records were retrieved for the same geographic boundary: Wayne County.

In addition to the two main study periods for Wayne County, we considered two other data sets for our secondary study objectives: 1981 to 1987, Wayne County multiple sites, TSP; and 1992 to 1994, Detroit–Ann Arbor–Flint

Consolidated Metropolitan Statistical Area (CMSA), PM_{10}. The 1981 to 1987 period was considered because a large number of TSP monitoring sites (14) operated during this period (although data were collected only every sixth day); this allowed us to investigate the effect of choice of monitoring site. The fourth data set, for 1992 to 1994, which had a larger geographic boundary, was used for a more detailed characterization of the data on hospital admissions of elderly patients; and a separate time-series analysis to investigate the effects of multiple admissions. The Detroit–Ann Arbor–Flint CMSA provided about twice as many daily counts as Wayne County.

Mortality Data Daily death counts for Wayne County MI between 1981 and 1990 and from 1992 through 1994, were extracted from the nationwide mortality records at the National Center for Health Statistics (NCHS). For quality control, we compared and verified the county-level annual total deaths in the extracted data with those listed in the *Vital Statistics of the United States* (US Department of Health and Human Services). Accidental deaths (*International Classification of Diseases, Ninth Revision* [ICD-9], codes ≥ 800) and deaths that occurred outside of the county of residence were excluded from this analysis. The daily deaths were aggregated for three categories of death as coded by ICD-9: total excluding injury and poisoning (< 800); circulatory (390–459); and respiratory (460–519). A fourth was calculated as the total nonaccidental mortality minus the combined deaths from circulatory and respiratory causes.

Hospital Admissions (Medicare Data) The Health Care Financing Administration's (HCFA's) Medical Provider Analysis and Review (MEDPAR) hospital discharge files for the state of Michigan were obtained for 1992 through 1994. Records were selected on the basis of age, facility type, type of admission, ICD-9 codes, and geographic boundaries.

Although the age of Medicare recipients is supposedly 65 or over, an initial data examination found a small fraction of records for patients younger than 65. We excluded those records. There are three types of facility recorded: short-stay, long-stay, and skilled nursing facilities. To be consistent with our assumption that the air pollution acutely affects and aggravates chronic conditions, we included records for short-stay hospitals only (approximately 90% of admissions). There were four possible types of admissions: emergency, urgent, elective, and newborn. Again, because our objective was to examine acute effects of air pollution, we included emergency and urgent admissions only.

The ICD-9 categories were chosen on the basis of our initial hypothesis and consistency with those analyzed in the past time-series studies. Because daily hospital admission counts were several times larger than the daily mortality counts, we could examine more detailed subcategories of ICD-9 divisions without compromising sample size. Initially we planned to analyze asthma admissions, but later chose not to include that category, in part because of its very small daily counts (such that it was not expected to achieve significance for the likely range of effect sizes), and in part because of comments from pulmonary physicians that asthma in the elderly could often be misdiagnosis of other COPD, making interpretation of results difficult. The ICD-9 respiratory categories chosen were pneumonia (ICD-9 480–486) and COPD (ICD-9 490–496); cardiovascular categories were ischemic heart disease (ICD-9 410–414), dysrhythmias (ICD-9 427), heart failure (ICD-9 428), and stroke (ICD-9 431–437).

As mentioned, two geographic boundaries were considered, Wayne County (for the main analysis) and the Detroit–Ann Arbor–Flint CMSA. The CMSA also included (1) the Ann Arbor PMSA: Lenawee, Livingston, and Washtenaw Counties; (2) the Detroit PMSA: Lapeer, Macomb, Monroe, Oakland, St Clair, and Wayne Counties; and (3) the Flint PMSA: Genesee County. The second (CMSA) boundary provided approximately twice the admission counts as those for Wayne County and was used for a detailed description of hospital admission patterns (eg, extent of multiple admissions, length of stay, mortality rate).

DATA ANALYSIS

Environmental Measurements Characterization

In addition to the usual correlation matrices of exposure variables, we conducted two environmental measurement-characterization analyses that could help the interpretation of health outcome analysis. These were site-to-site temporal correlation and factor analysis.

Site-to-Site Temporal Correlation Past observational studies that analyzed multiple air pollutants (and weather variables) often interpreted the strength of association as the strength of causality. This is adequate only if all the air pollution and weather variables are measured equally precisely. The temporal error that can affect the population-level short-term exposure-response relation actually has several components including instrumental or analytical error, the discrepancy in temporal fluctuations between a person and a monitor, and the monitor-to-monitor discrepancy in temporal fluctuations. The instrumental and analytical errors are embedded in both the person-to-

monitor and monitor-to-monitor errors. It is possible that the apparent consistency of associations between PM and mortality versus less consistency for other pollutants (eg, SO_2) simply reflects the higher spatial uniformity for PM. In this project, the only component of error that could be investigated was the monitor-to-monitor discrepancy, based on site-to-site temporal correlation among multiple pollution monitoring sites.

Pairwise Pearson correlation coefficients were calculated for all available pairs for each of the air pollution indices for all available days between 1981 and 1994. Their corresponding separation distance was also calculated, based on longitude-latitude information, in order to determine if the correlation was dependent on their separation. Used in this calculation were 8 sites for PM_{10}, 24 sites for TSP, 23 sites for SO_2, 4 sites for O_3, 5 sites for NO_2, and 11 sites for CO. This analysis could not be conducted for variables that did not have multiple monitoring stations (ie, $PM_{2.5}$, H^+, and SO_4^{2-}).

Factor Analysis Factor analysis is a multivariate procedure to examine relations among many variables. Usually the goal is to find a parsimonious underlying structure in multivariate data. Each variable is reexpressed as a linear combination of the underlying (and possibly causal) factors. Factor analysis may be used to reduce the number of explanatory variables in regressions. For our application, however, each variable contributes to an explanation of common pollution and weather factors. Each of the pollution or weather variables can then be expressed as a linear combination of the common factors, using days as observations:

$$X_{ik} = \sum_{j=1}^{p} W_{ij} F_{jk}$$

in which X_{ik} (input) is a standardized z-score (ie, centered and divided by its standard deviation) of the ith pollution or weather variable on the kth day (observation), F_{jk} (output) is the jth factor on the kth day, and W_{ij} (output) is the scoring coefficient ($1 \le W_{ij} \le 1$), which indicates the extent of (positive or negative) dependence (or correlation) of the variable X with that factor F. Thus, the matrix of the coefficient W, called factor loadings (in which the row is a variable and column is a factor), depicts the pattern of clustering, showing which group of variables fluctuates together over time. Note that in this study we use factor analysis as an exploratory tool, but not to quantitatively apportion particle mass to specific sources. We did not conduct quantitative emission inventories for Wayne County.

Health Outcome Characterization

We explored the data on mortality and hospital admissions of elderly patients in order to help develop adequate health outcome regression models in the next stage and to assure the careful interpretation of results from the health outcome regressions. For the first purpose, we computed power spectra of mortality and hospital admission time series so that the relative importance of seasonal cycles, day-of-week effects, and random components could be observed. For the second purpose, we examined aspects of the detailed individual records for Medicare such as the extent of multiple admissions, length of stay, and mortality rates in each of the ICD-9 categories.

Health Effects Models

Poisson (log-linear) regressions were used to model the health outcome variables as a function of air pollution, weather, and temporal trends. In order to model nonlinear relationships with exposure variables and temporal trends, generalized additive models (GAM) (Hastie and Tibshirani 1990) were used to extend the Poisson model:

$$\log[E(Y)] = \sum_{i=1}^{p} S_i(X)_i$$

in which E denotes expected values; Y is a health outcome variable (mortality or hospital admission); X_i is the ith explanatory variable; and $S_i(X_i)$ is the smooth function of the ith explanatory variable, using either locally weighted smoothing scatterplots (LOESS) (Cleveland 1979) or other smoothing methods (Hastie and Tibshirani 1990). Linear terms were used for pollutants so that relative risk could be calculated for a given increment of the pollutants.

Basic Poisson regression models included three stages.

1. Adjustment for confounding time trends (annual cycles, influenza epidemics) by smoothing of mortality or hospital admission series over time. The smoothing period was selected on the basis of residual overdispersion and autocorrelation. We used smoothing splines (on days) as implemented in S-PLUS (MathSoft, Seattle WA), in part because this method has characteristics of linear filters (Hastie and Tibshirani 1990) and thus makes it easier to interpret model behavior in terms of a moving average.
2. Development of alternative temperature and humidity model specifications and selection of the best model. The criteria for choosing a model are consistency with prior knowledge of biological plausibility (right signs); significance of coefficients; and Akaike Information Criterion (AIC). We used AIC only when we

Table 2. Distribution of All Variables Between 1985 and 1990[a]

	n Days	5%	25%	50%	75%	95%	Mean
Total deaths/day	2,191	37	44	49	54	63	49
Respiratory deaths/day	2,191	1	2	4	5	7	3.7
Circulatory deaths/day	2,191	16	21	25	29	35	25
Total – (resp. + circ.) deaths	2,191	13	17	20	23	28	20.4
PM_{10} avg ($\mu g/m^3$)	1,565	16	28	40	59	92	45.4
TSP (site y) ($\mu g/m^3$)	1,762	29	47	63	84	125	68.7
TSP–SO_4^{2-} (site y) ($\mu g/m^3$)	1,759	4.8	7.8	10.2	13.6	22.6	11.5
O_3 avg (ppb)	1,827	5.0	12.0	19.5	27.5	41.0	20.9
SO_2 avg (ppb)	2,191	3.7	6.1	8.9	12.6	19.4	9.8
NO_2 avg (ppb)	1,569	11.0	17.0	22.5	29.0	39.0	23.3
CO × 10 avg (ppm × 10)	2,184	4.6	6.3	8.0	10.6	16.1	9.0
Mean temp (°F)	2,191	18	35	51	66	77	49.9
Mean relative humidity (%)	2,191	51	64	71	80	90	71.3

[a] The values for gaseous pollutants are the daily average of 24 hourly measurements.

had no a priori preference for one model over another in terms of the other two criteria.

3. Introduction of air pollution variables (0-day lag through 3-day lag, and multiday averages thereof) individually in the above model and evaluation of optimum lag, significance, and model fit. In presenting results for all the pollutants, we used the 5th to 95th percentile of each pollutant to compute relative risk. Two pollutant models also were examined using the optimal lag selected in the single pollutant models.

RESULTS

1985–1990 STUDY, PM COMPONENTS: PM_{10}, TSP, AND TSP–SO_4^{2-}

Table 2 shows the distribution of all the variables used in the analysis of the 1985 to 1990 study period. The gaseous pollutants and PM_{10} are the average values of multiple monitoring sites. Values for PM_{10} were, on average, 66% of TSP mass, and TSP–SO_4^{2-} was 25% of PM_{10} mass. No systematic pattern was obvious in the missing values of these pollution variables, except in the case of O_3, which was collected only in the warm season (April to October) from November 1988 onward. In comparing average effects of each pollutant, we used the mortality relative risk (or rate ratio) per 5th to 95th percentile increment of each air pollution index. This increment was selected because it gives a sense of the low to high pollution range.

Table 3. Correlation Among Covariates

	PM_{10}	TSP	TSP–PM_{10}	TSP–SO_4^{2-}	O_3	SO_2	NO_2	CO	Temperature
TSP	0.63								
TSP–PM_{10}	–0.18	0.66							
TSP–SO_4^{2-}	0.48	0.59	0.33						
O_3	0.36	0.36	0.18	0.30					
SO_2	0.47	0.32	–0.01	0.27	–0.06				
NO_2	0.53	0.40	0.03	0.30	–0.01	0.52			
CO	0.35	0.28	0.02	0.18	–0.22	0.36	0.58		
Temperature	0.36	0.32	0.13	0.29	0.62	–0.08	0.02	–0.08	
Relative humidity	–0.05	–0.23	–0.30	0.24	–0.41	0.01	0.07	0.14	–0.12

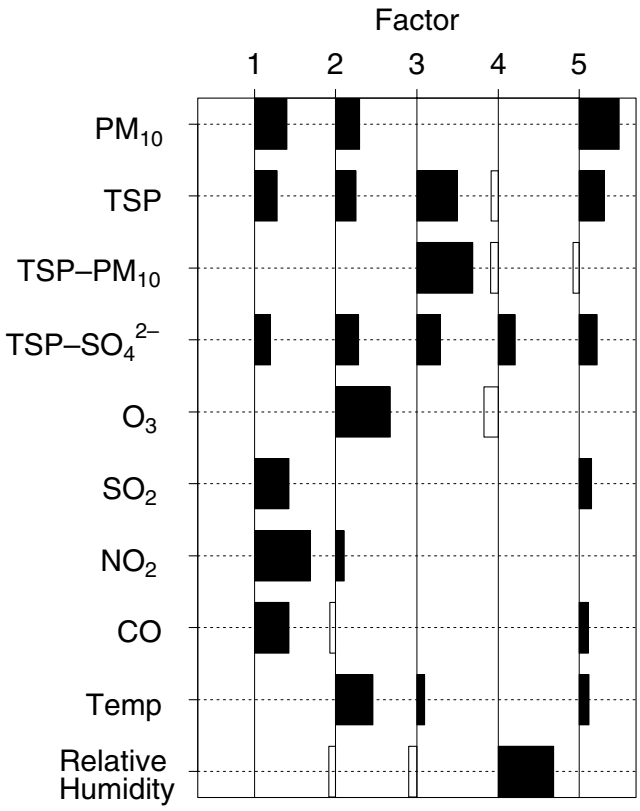

Figure 2. Factor loadings for 1985 to 1990 data variables. Black bars are proportional to positive loadings; white bars are proportional to negative loadings. Each series was de-trended with periodicity of approximately one month prior to factor analysis.

Environmental Measurements Characterization

Table 3 shows a correlation matrix of the environmental covariates. PM_{10} and TSP were moderately correlated. Once PM_{10} mass was subtracted from TSP, the remainder was still correlated with TSP, but not with PM_{10}. The correlations of O_3 and CO with PM_{10} and TSP were relatively small (0.3 to 0.35), but SO_2 and NO_2 were mildly correlated (~0.5) with PM_{10}.

A factor analysis may help to further depict the relations among these exposure variables. Figure 2 shows the factor loadings of these covariates. Because we did not conduct quantitative emission inventories for this locale, we do not attempt to name these factors. However, it can be seen that PM components have loadings on multiple factors, except for $TSP–PM_{10}$, which has a loading shared only by TSP. The first factor may be general air pollution due to air stagnation, whereas the second factor, with its loadings on O_3 and temperature, may be summer haze–type pollution.

Figure 3 shows the resulting correlation versus separation distance for all the air pollution indices. All sites were located within 30 miles of others. It can be seen that correlation is weakly dependent on separation distance for TSP and SO_2. The high correlation among the O_3 sites is notable. The highest correlation that can be achieved appears to be limited to about 0.8 for any pollutant, and although this can be achieved by a pair separated by 20 miles, a pair of sites separated by only 5 miles can have a correlation as low as 0.1. Disregarding the variable length of periods in which different pollution indices were available, the order of spatial uniformity, in terms of temporal fluctuations as expressed by the median correlation was O_3 (0.83), PM_{10} (0.78), TSP (0.71), NO_2 (0.70), CO (0.50), and SO_2 (0.49).

Mortality Model Development and Results

Adjustment for Seasonal Cycles We first examined the choice of time window to control for seasonal cycles. We did this using the longer 1981 to 1990 period, rather than the 1985 to 1990 period, in order to extract and use as much information as possible. Although we would have preferred to control for time-trend periodicity longer than about one month (to avoid influenza epidemics and annual sinusoidal waves), we examined the residual overdispersion and first-order autocorrelation in the Poisson regression of each mortality series on smoothing splines over time (days) using smoothing periods ranging from 1 year to 15 days. Day-of-week dummy variables also were included, because the day-of-week pattern can further contribute to overdispersion. The results are plotted over the equivalent moving-average time window (number of observations/degrees of freedom [*df*]).

Figure 4 shows the result for total (nonaccidental) deaths. The overdispersion could be reduced from 1.3 (no control) to 1.01 by controlling for periodicity that is longer than one month. As can be seen in the plot, however, controlling for short periodicity (down to 15 or 21 days) resulted in underdispersion as well as negative autocorrelation, which indicates overcontrol for long waves. We obtained similar results for the circulatory series. Thus we concluded that, for the total and circulatory series, the use of smoothing splines with an equivalent moving average of 31 days (one month) was adequate. For the respiratory series, however, adjustment for this periodicity resulted in underdispersion, again indicating overadjustment for residual variation. An equivalent moving average of 90 days produced an adequate dispersion parameter; therefore, for the respiratory series, we employed smoothing splines with degrees of freedom that correspond to this cutoff.

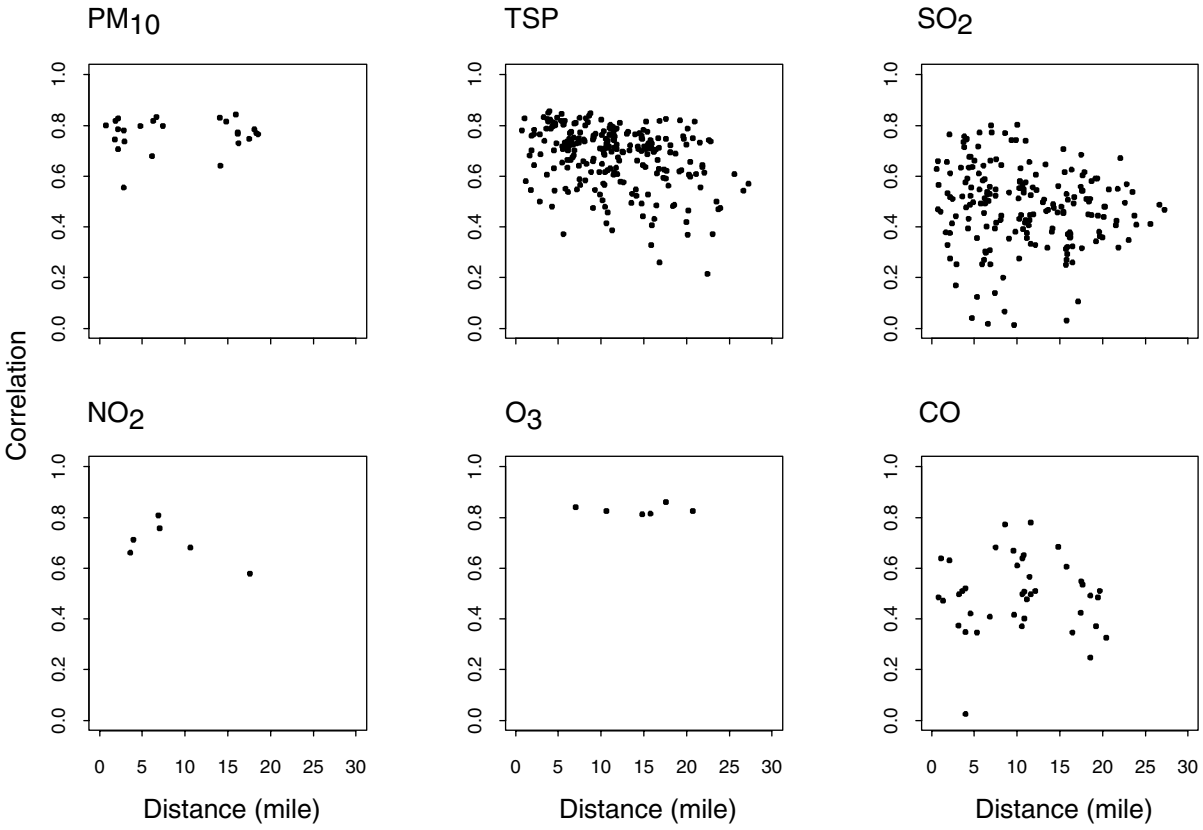

Figure 3. Site-to-site temporal correlation of multiple pollution sites.

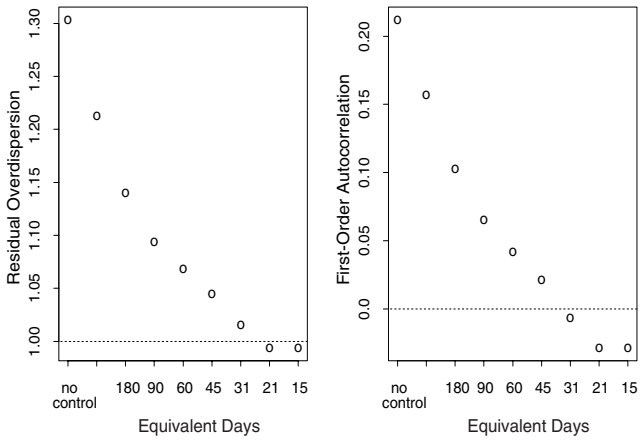

Figure 4. Total mortality series residual overdispersion and first-order autocorrelation as a function of equivalent time window for smoothing to control for seasonal cycles and other shorter temporal trends.

Weather Models With the above-mentioned smoothing splines in the Poisson model, we next examined various temperature and humidity parameters. Again, the analysis was done using the 1981 to 1990 period. Our preliminary results indicated that 2-day lagged temperature variables usually were associated most significantly and negatively with mortality and that same-day temperature variables were associated positively with mortality. These associations were nonlinear, and we therefore used LOESS smoothing of mortality over the same-day temperature (span = 0.5) and 2-day lagged temperature (span = 0.5); and the squared deviation from 60°F, for the same-day temperature and 2-day lagged temperature, of two temperature variables. Our preliminary results also showed that a hot (mean temperature ≥ 80°F) and humid (relative humidity ≥ 70%) day was a significant predictor of mortality. Thus, we specified models with several combinations of these variables.

Table 4. Weather Model Specifications and Resulting AIC and Overdispersion Parameter for Total Mortality Series (Time Trend Included)

Model Number	Model Specification	AIC	Dispersion
1	LOESS of same-day temperature	3,787	1.034
2	LOESS of same-day temperature and 2-day lagged temperature	3,779	1.031
3	2 + hot-and-humid indicator	3,776	1.030
4	2 + 1-day lagged hot-and-humid indicator	3,779	1.031
5	two squared deviation (from 60°F) variables[a]	3,761	1.026
6	LOESS of same-day humidity	3,828	1.044
7	LOESS of 1-day-lagged humidity	3,833	1.046
8	2 + 6	3,778	1.031
9	2 + 7	3,779	1.031
10	5 + hot-and-humid indicator	3,761	1.025

[a] IF temperature ≤ 60 THEN hot_sqr = 0; ELSE hot_sqr = (temperature − 60)^2; and IF 2-day-lagged temperature ≤ 60 THEN cold_sqr = (60 − 2-day-lagged temperature)^2; ELSE cold_sqr = 0.

The AIC and dispersion parameters for some of these regression results are shown in Table 4 to illustrate relative contributions from these variables. Both the AIC and the dispersion parameter suggested that models 5 and 10 were the best candidates. However, in these models the smoothing splines showed an overall negative coefficient, which is not reasonable. In other cases we observed that smaller AICs do not necessarily result in biologically rational models. This likely is due to correlation among the covariates chosen. Therefore, we chose model 3, on the basis that all of the variables were significant and had the "right" signs; its biological plausibility is consistent with our knowledge, and it yielded the second-smallest AICs.

We next introduced pollution variables, lags 0 through 3 days, one at a time, into the Poisson regression with the weather model specifications described above. The lag structure of associations between PM components and the three mortality series was generally consistent, with the 1-day lagged PM_{10}, TSP, and TSP–SO_4^{2-} having the largest positively significant point estimates. Figure 5 shows the results for respiratory mortality in association with with PM_{10}, TSP, and TSP–PM_{10} (results for all the pollutant lags are shown in Appendix C).

Note that multiple lag days show positive associations. Because these positive and marginally significant coefficients (and borderline nonsignificant coefficients) are distributed over 0- to 2-day lags, it may be justified to take the average of these three days. However, when we additionally considered multiday-average pollution indices (ie, average of 0 and 1 days, 1 and 2 days; up to 4-day averages of 0- through 3-day lags), the estimated relative risks per 5th to 95th percentile increment were comparable to those for single-day-lag results. (The multiday-average results

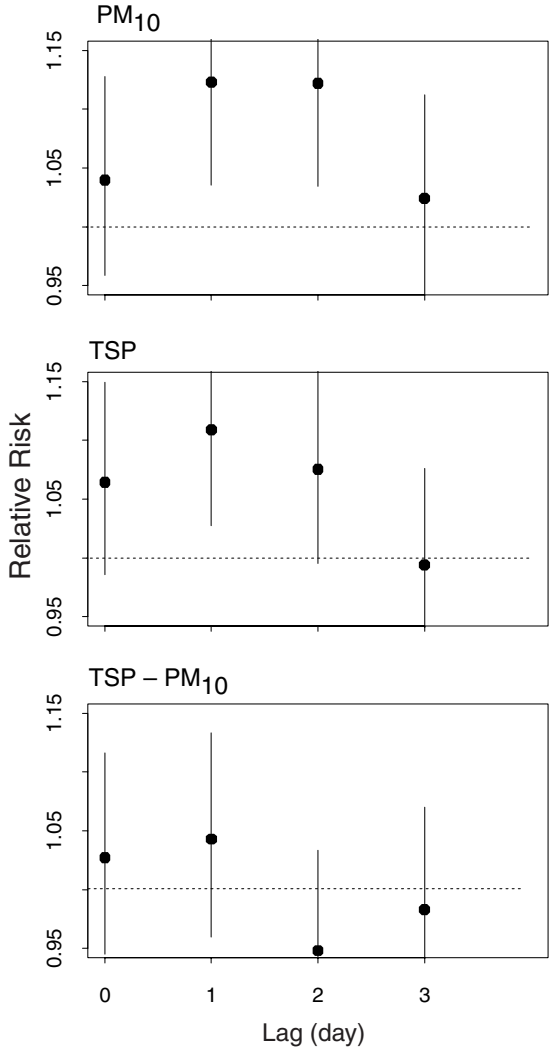

Figure 5. Respiratory mortality relative risk per 5th to 95th percentile increment of PM indices for lag days 0 through 3.

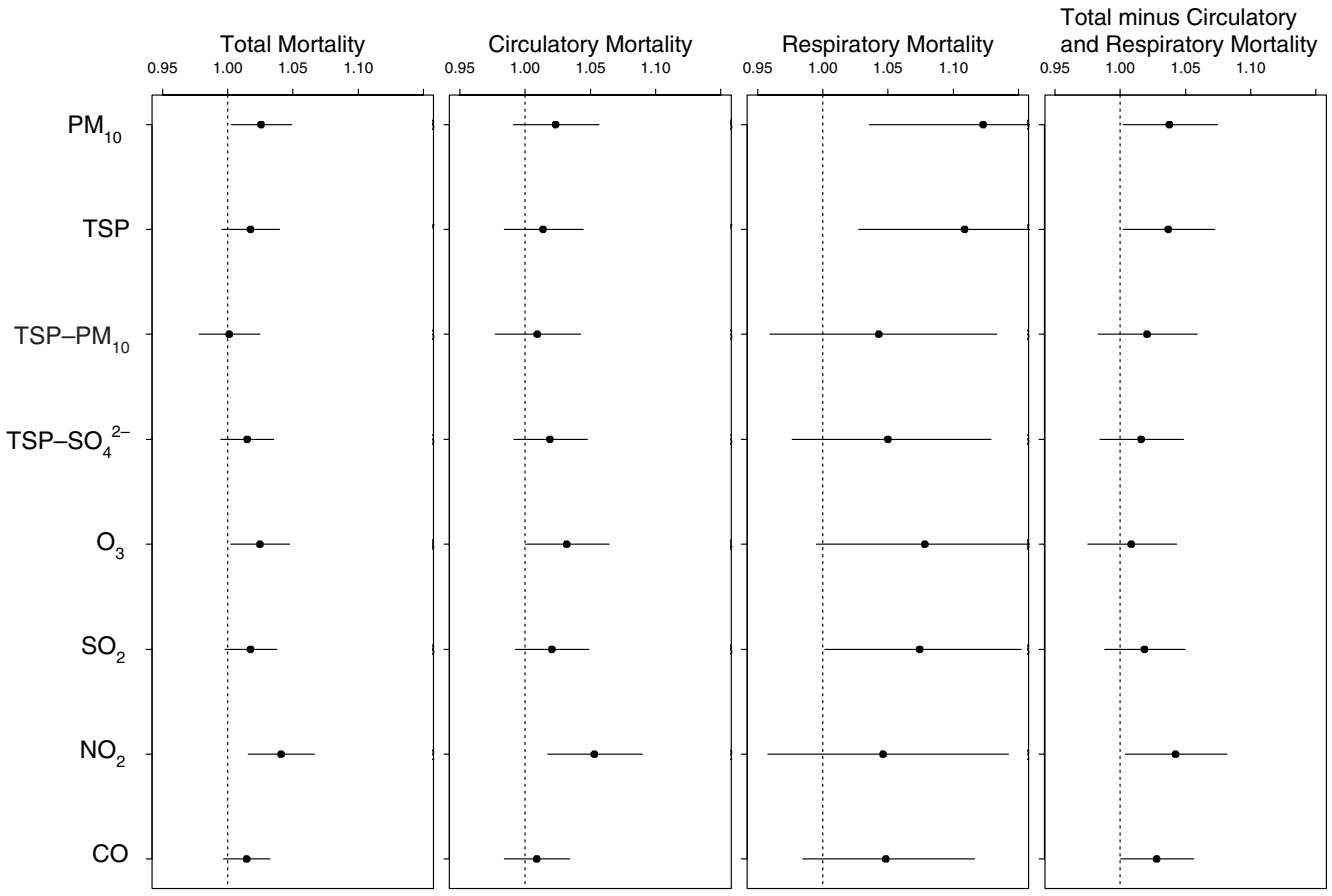

Figure 6. Mortality outcomes. Relative risks per 5th to 95th percentile pollution increment.

for all the pollutants are shown in Appendix C [1985–1990] and Appendix D [1992–1994].) Therefore, in response to our main question regarding relative associations among the PM components, we mainly report single-day-lag results.

Figure 6 shows the estimated relative risks per 5th to 95th percentile increment for respiratory, circulatory, total, and total minus circulatory and respiratory mortality series for single-day pollution indices. Most significant and largest relative risks are seen in the respiratory series. Note that the relative risks for total minus circulatory and respiratory mortality were also associated with pollution indices. This is a somewhat surprising result because respiratory and circulatory problems commonly are hypothesized to be effects of air pollution. We point out, however, that the time-series plot (not shown) of the total minus circulatory and respiratory mortality exhibited seasonal cycles and apparent influenza peaks, suggesting that this series also is influenced by respiratory (contributing) causes.

Table 5. Total Mortality and Relative Risks (95% CI) for PM Indices per 5th to 95th Percentile Increment

Pollutant	PM Alone	With O_3 (Lag 1)	With SO_2 (Lag 2)	With NO_2 (Lag 2)	With CO (Lag 3)
PM_{10} (lag 1)	1.026 (1.003–1.049)	1.028 (1.001–1.055)	1.023 (1.000–1.047)	1.022 (0.994–1.052)	1.023 (1.000–1.046)
TSP (lag 3)	1.018 (0.996–1.040)	1.015 (0.992–1.040)	1.016 (0.994–1.039)	1.030 (1.002–1.060)	1.014 (0.992–1.038)
TSP–PM_{10} (lag 1)	1.001 (0.978–1.025)	1.005 (0.980–1.031)	1.001 (0.978–1.025)	0.991 (0.964–1.020)	1.002 (0.979–1.025)
TSP–SO_4^{2-} (lag 3)	1.015 (0.995–1.035)	1.010 (0.989–1.031)	1.015 (0.995–1.035)	1.018 (0.992–1.044)	1.012 (0.992–1.033)

Table 6. Circulatory Mortality and Relative Risks (95% CI) for PM Indices per 5th to 95th Percentile Increment

Pollutant	PM Alone	With O_3 (Lag 1)	With SO_2 (Lag 3)	With NO_2 (Lag 2)	With CO (Lag 3)
PM_{10} (lag 3)	1.023 (0.991–1.057)	1.021 (0.985–1.059)	1.013 (0.977–1.051)	1.036 (0.997–1.076)	1.019 (0.985–1.055)
TSP (lag 3)	1.014 (0.984–1.045)	1.007 (0.974–1.040)	1.005 (0.974–1.037)	1.030 (0.991–1.071)	1.012 (0.981–1.044)
TSP–PM_{10} (lag 1)	1.009 (0.977–1.043)	1.015 (0.980–1.051)	1.008 (0.976–1.041)	0.996 (0.958–1.036)	1.010 (0.978–1.043)
TSP–SO_4^{2-} (lag 2)	1.019 (0.991–1.048)	1.014 (0.984–1.044)	1.015 (0.987–1.044)	1.029 (0.994–1.065)	1.019 (0.991–1.048)

Table 7. Respiratory Mortality and Relative Risks (95% CI) for PM Indices per 5th to 95th Percentile Increment

Pollutant	PM Alone	With O_3 (Lag 2)	With SO_2 (Lag 2)	With NO_2 (Lag 3)	With CO (Lag 2)
PM_{10} (lag 1)	1.123 (1.036–1.218)	1.080 (0.983–1.186)	1.107 (1.018–1.204)	1.108 (1.008–1.219)	1.116 (1.026–1.214)
TSP (lag 1)	1.109 (1.028–1.197)	1.097 (1.008–1.194)	1.102 (1.020–1.190)	1.097 (0.999–1.203)	1.097 (1.014–1.185)
TSP–PM_{10} (lag 1)	1.043 (0.960–1.133)	1.044 (0.953–1.143)	1.044 (0.961–1.135)	1.039 (0.941–1.148)	1.047 (0.964–1.138)
TSP–SO_4^{2-} (lag 1)	1.050 (0.976–1.129)	1.040 (0.963–1.122)	1.040 (0.965–1.120)	1.022 (0.932–1.121)	1.036 (0.962–1.116)

Table 8. Data Distribution of 14 TSP Sites Between 1981 and 1987

Site	Days	5%	25%	50%	75%	95%	Mean	Land Use[a]	Location Setting[b]	Median r [c]	r With Site y
a	395	25	44	60	79	127	66	COM	SUB	0.73	0.65
b	380	47	77	107	144	224	118	IND	SUB	0.55	0.54
c	411	16	29	42	60	95	48	COM	SUB	0.66	0.59
d	393	30	49	66	90	139	74	IND	SUB	0.70	0.57
f	403	19	31	42	60	86	47	RES	SUB	0.74	0.63
g	396	43	67	84	114	188	97	COM	URB	0.72	0.62
h	407	25	42	58	82	132	65	RES	URB	0.73	0.59
i	404	26	42	54	74	121	61	RES	SUB	0.73	0.69
j	377	24	40	54	78	114	61	COM	SUB	0.72	0.65
k	392	21	34	48	67	114	55	RES	SUB	0.76	0.60
v	397	18	30	44	61	90	48	RES	SUB	0.72	0.66
w	395	22	39	51	70	101	57	COM	SUB	0.61	0.61
x	411	25	39	51	70	112	58	COM	SUB	0.74	0.63
y[d]	377	29	47	62	83	125	66	NA	NA	0.62	NA

[a] Land-Use keys: COM: Commercial; IND: Industrial; RES: Residential.

[b] Location-Setting Keys: SUB: Suburban; URB: Urban; NA = not available.

[c] Median temporal correlation with other sites.

[d] The Canadian site in Windsor had daily values, but only every-6th-day schedule days were used.

We next considered two-pollutant models, using one of the PM indices and one of the gaseous pollutants at a time. For the gaseous pollutants, the lags that gave the most significant coefficients varied; therefore, we included those lags. Tables 5 through 7 show the resulting relative risks. Note that the addition of the gaseous pollutants does not always reduce PM coefficients. The largest reduction of a PM coefficient was that for PM_{10} with respiratory mortality when O_3 was included (1.123 to 1.080).

1981–1987 STUDY OF THE EFFECTS OF THE CHOICE OF PM MONITORING SITES

The motivation for this analysis came from our initial concern about the adequacy of the PM monitoring sites used in the main analyses. For example, if the results are sensitive to the choice of PM monitoring site(s), then it would be difficult to draw any inference from a set of results obtained using a single PM monitoring site. Multiple PM monitoring sites with extensive data were not available for the two main study periods (1985 to 1990 and 1992 to 1994). However, on the basis of the initial data inventory, we identified a period, 1981 to 1987, when 14 TSP monitoring sites, including site y in Windsor, operated with no major fraction of missing data. Multiple monitoring sites with comparably complete data were not available for other pollutants. Thus, we conducted time-series analyses using each one of these 14 TSP sites and examined the range of estimated relative risks. We examined only total (nonaccidental) mortality. Table 8 shows the data distribution for these 14 TSP sites. The site labels are the same as those presented in Table 1. Note that the number of available days, even though measurements were made only every sixth day, is comparable. However, the mean levels at these sites varied by a factor of two. The mean (66 $\mu g/m^3$) of site y (the Canadian site from which we used the data in the previous analysis) is slightly higher than the median (61 $\mu g/m^3$) of these 14 mean levels.

We applied the basic total mortality model developed in the 1985 to 1990 analysis to each of the 14 sites. Thus, the covariates included smoothing splines with time windows equivalent to a 1-month period to adjust for long-wave temporal trends, LOESS smoothing of the same day, and the average temperature for the past 1 to 3 days day-of-week dummy variables. Lags 0 through 3 days of each TSP site's data were examined, and relative risks were computed for the 5th to 95th percentile increment. We also calculated site-to-site temporal correlation for every pair of sites, determined for each site the median site-to-site correlation with other sites, and examined the relation between the median correlation and the estimated relative risks.

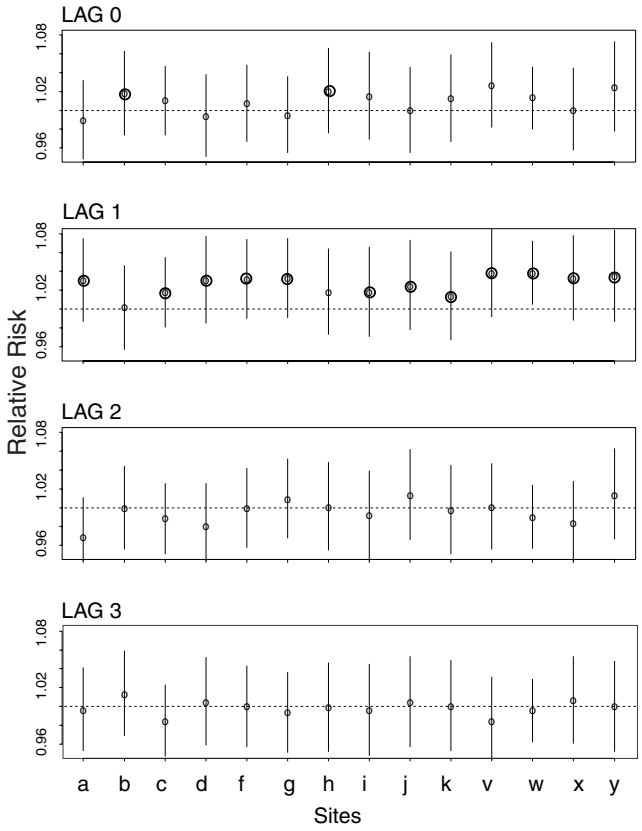

Figure 7. Relative risks estimated for each of the 14 TSP sites (lags 0 through 3 days). The largest relative risks for each site across the 4 lag days are circled.

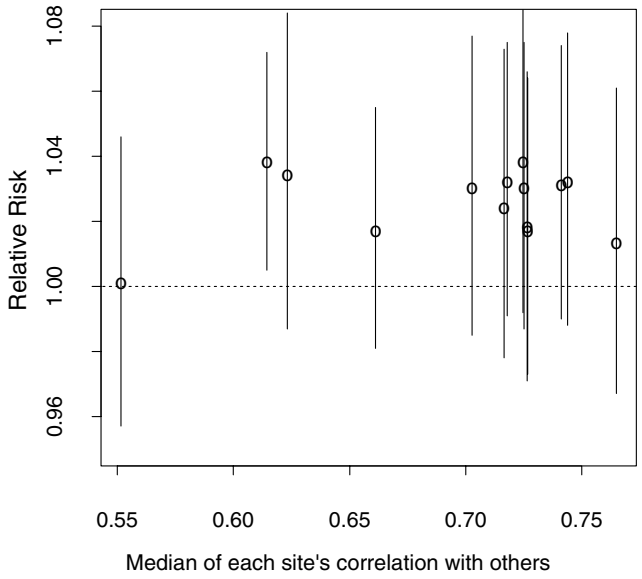

Figure 8. The estimated relative risk for each of the 14 TSP sites versus corresponding median site-to-site correlation.

Figure 7 shows the resulting relative risks for the 14 TSP sites for lags 0 through 3 days. Note that, of the 14 sites, 12 had the highest relative risks on a 1-day lag (the two others had the highest relative risks on the 0-day lag). These relative risks on the 1-day lag are mostly comparable, and the distribution of their point estimates appears to be tighter than those of the 95% CIs obtained from the regression models. However, recall that the mean levels for these sites varied by a factor of two. For example, the 5th to 95th percentile increment of site f is 67 $\mu g/m^3$, and that for site g is 145 $\mu g/m^3$. The fact that the calculated relative risks for sites f and g for the 1-day lag appear identical (see Figure 7) indicates that the regression coefficient for site f was about twice as large as that for site g (in fact, they were 0.00046 versus 0.00022, respectively). Thus, the raw coefficients among the multiple TSP sites did vary, but the distributional increments to calculate relative risk tend to standardize the scale of relative risks. This actually makes sense in that if there is a concentration gradient of TSP within a city, and if the various TSP concentrations fluctuate together, then using a site with low mean TSP for time-series analysis would result in a larger coefficient. This result does warn against extrapolating the effects from one city to another using a raw regression coefficient.

Figure 8 shows the relation between each site's median site-to-site correlation versus corresponding relative risk on lag 1-day. Although the range of correlation was not large (0.55 to 0.77), there was no apparent relation between a site's temporal correlation with others and its relative risk, except at site b. Site b had the poorest correlation with other sites but also had the lowest relative risk. Using the lag with the highest relative risk, rather than fixing the lag on day 1, would eliminate such an exception. Site b also had the largest mean and standard deviation. These results suggest that the estimated TSP relative risks per a given distributional increment were not sensitive to the choice of site in these data, and that the Windsor site was as good as any other sites in the area in terms of representing the population TSP exposure for the Detroit metropolitan area.

Table 9. Distribution of Air Pollution and Weather Variables for 1992 through 1994[a]

	n Days	5%	25%	50%	75%	95%	Mean	Max
PM_{10} (μg/m^3)	490	12	19	28	38	63	31	105
$PM_{2.5}$ (μg/m^3)	490	6	10	15	21	42	18	86
$PM_{10–2.5}$ (μg/m^3)	490	4	8	12	17	28	13	50
H^+ (nmole/m^3)	344	0	0	2	7	40	8.8	279
SO_4^{2-} (nmole/m^3)	344	9	19	33	66	174	54	359
O_3 avg (ppb)	549	11	18	23	30	39	25	55
SO_2 avg (ppb)	1,096	2	3	6	9	15	7.0	28
NO_2 avg (ppb)	1,090	11	16	21	26	36	21.3	55
CO × 10 avg (ppm × 10)	1,096	3.6	4.8	6.2	8.0	12	7.2	39
Mean temperature (°F)	1,096	20	36	51	65	76	50	87
Mean relative humidity (%)	1,096	51	64	71	79	90	71	99

[a] The values for pollutants are daily 24 hourly values.

1992–1994, WAYNE COUNTY: PM_{10}, $PM_{2.5}$, $PM_{10–2.5}$, SO_4^{2-}, AND H^+

Environmental Measurements Characterization

Table 9 shows the distribution of all the variables used in this analysis. The PM components from the Windsor site were collected daily from May to September, and less frequently during the rest of the year (every third day from September 20, 1992, to April 30, 1993; every sixth day from September 20, 1993, to April 30, 1994). To compare the results for gaseous pollutants on a same-sample-size basis, we present the regression results for those cases restricted to the days when size-fractionated PM data were available (n = 490). Note that H^+ and SO_4^{2-} have an even smaller number of days available (344 days). To conduct a fair comparison among the PM indices, the health effects analyses included only the period when H^+ and SO_4^{2-} data were available.

Table 10 shows intercorrelation among the covariates. The correlation for each pair was calculated with available cases for that pair, rather than using available cases common to all the variables. It should be noted that, because there are more available days during summer for PM components and O_3, the correlation among the summer-type pollutants is likely lower than it would have been with the year-round data set (because of the lack of summer versus winter variance). It can be seen that PM_{10} is highly correlated (r = 0.9) with $PM_{2.5}$ in this data set, more so than with $PM_{10–2.5}$ (r = 0.77). Intercorrelation among H^+, SO_4^{2-}, and $PM_{2.5}$ is also relatively high (0.6 to 0.8). Correlation of the gaseous pollutants with PM components generally was weaker ($r < 0.5$), with the highest correlation observed between O_3 and SO_4^{2-} (0.52). Correlation between weather variables and pollutants also was relatively low ($r < 0.5$).

Table 10. Correlation Among Covariates

	PM_{10}	$PM_{2.5}$	$PM_{10–2.5}$	H^+	SO_4^{2-}	O_3	SO_2	NO_2	CO	Temperature
$PM_{2.5}$	0.90									
$PM_{10–2.5}$	0.77	0.42								
H^+	0.48	0.65	0.02							
SO_4^{2-}	0.68	0.84	0.14	0.78						
O_3	0.47	0.49	0.25	0.45	0.52					
SO_2	0.34	0.40	0.13	0.27	0.43	0.29				
NO_2	0.49	0.48	0.32	0.14	0.35	0.14	0.53			
CO	0.38	0.38	0.24	0.16	0.32	0.16	0.42	0.68		
Temperature	0.43	0.35	0.37	0.26	0.31	0.47	–0.05	0.02	–0.03	
Relative humidity	0.02	0.19	–0.24	0.13	0.20	–0.27	0.03	0.04	0.09	–0.02

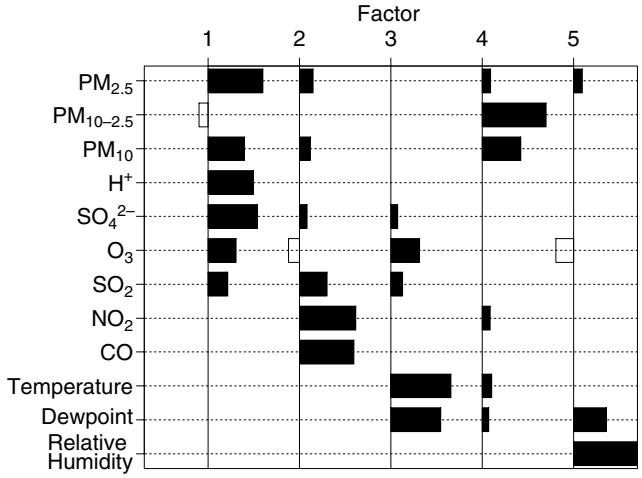

Figure 9. Factor loadings for 1992–1994 exposure variables. Black bars are proportional to positive loadings; white bars are proportional to negative loadings. Each series was de-trended with periodicity of approximately one month prior to factor analysis.

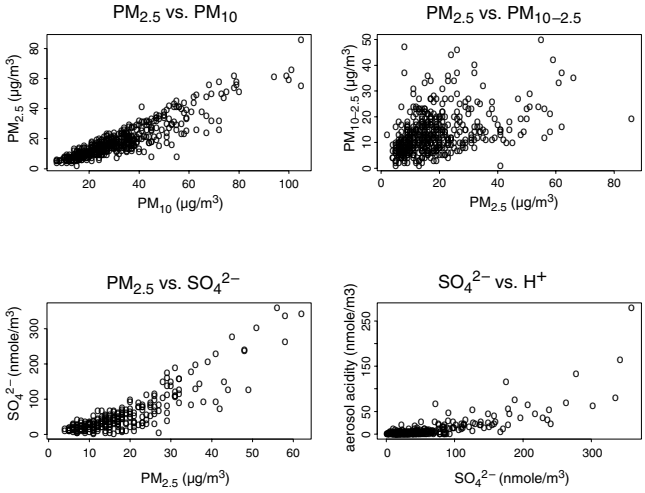

Figure 10. Scatterplots of key PM components.

Figure 9 shows the results (factor loadings) from a factor analysis of all the exposure variables. Again, without a detailed emission inventory, we cannot definitively name the factors. However, it can be seen that the first factor has large loadings on the summer haze–related PM components, with smaller loadings on O_3 and SO_2. The pattern of loadings on factor 1 may be characterized as the secondary aerosol factor. Factor 2, which may be characterized as the primary pollution factor, is shared by NO_2, CO, and SO_2. Note that the coarse fraction of PM_{10} had its own factor.

Scatterplots of the key PM components are shown in Figure 10. On average, 60% of PM_{10} mass was from $PM_{2.5}$. On high-$PM_{2.5}$ days, up to 50% of $PM_{2.5}$ can be attributed to SO_4^{2-}, but on lower-$PM_{2.5}$ days (< 20 µg/m^3), smaller fractions (< 25%) were due to SO_4^{2-}. High-SO_4^{2-} days tended also to be high-H^+ days, but when SO_4^{2-} levels were lower (ie, < 100 nmol/m^3), H^+ levels were essentially below the detection limit. In fact, 85% of H^+ data was below the detection limit (8 nmol/m^3) for the measurement system used.

Table 11. Distribution of Daily Mortality and Hospital Admissions in Wayne County, Michigan, for 1992–1994

Category	25%	50%	75%	Mean	Max
Total mortality	47	52	58	53	86
Circulatory mortality	21	24	28	25	45
Respiratory mortality	3	4	6	4	12
Total – (circ + resp)	21	24	27	24	42
Pneumonia admissions	9	11	14	12	42
COPD admissions	6	8	10	8	31
Ischemic heart disease admissions	18	21	26	22	40
Dysrhythmias admissions	5	7	9	7	19
Heart failure admissions	13	17	21	17	34
Stroke admissions	11	13	16	13	27

Mortality and Hospital Admission Model Development and Results

The data distributions of the mortality and elderly hospital admissions are shown in Table 11. Smoothed (smoothing splines equivalent to 31-day moving-average filter) time series of all the health outcomes illustrate the difference and similarity in seasonal patterns among the mortality and morbidity outcomes (Figure 11). Clearly, mortality from both circulatory and respiratory causes as well as hospital admissions for respiratory illness (pneumonia and COPD) were strongly influenced by influenza epidemics, whereas hospital admissions for cardiovascular problems were not. This is an interesting observation because it illustrates the extent of the impact that viral respiratory infections have on mortality from circulatory causes and their lack of impact on hospital admissions in more specific cardiovascular categories. In respiratory categories, hospital admissions tend to be lowest during summer. In circulatory categories, seasonal cycles were not obvious; the exception was heart failure, which exhibited seasonal cycles with the highest admissions in early spring. Note also that, as exhibited clearly in the 1993 to 1994 influenza peaks, a lag of about one to two weeks occurred in the peaks between the respiratory-related admissions and respiratory-related mortality. The time lag

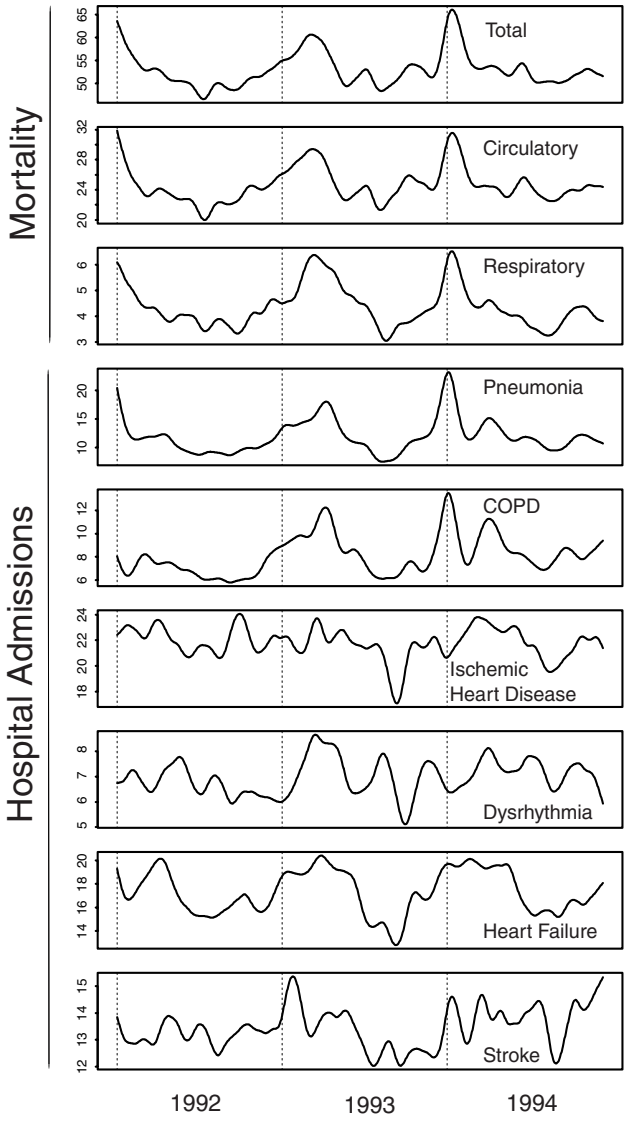

Figure 11. Seasonal and subseasonal trends fitted for outcomes. Smoothed health outcome time series.

between admissions and deaths may provide insight into the relation between the morbidity effects and mortality effects of air pollution. This issue was further investigated and is discussed in Appendix A.

Another feature present in some of the health outcome time series, especially prominent in hospital admissions, is the high-frequency repeating day-of-week pattern; admissions are higher on Monday, gradually decline toward the weekend, and drop sharply on Saturday and Sunday. This pattern is evident in all the categories but is most prevalent in hospital admissions for ischemic heart disease and dysrhythmias. Relative variance contributions from seasonal cycles, influenza outbreak, and a day-of-week pattern can

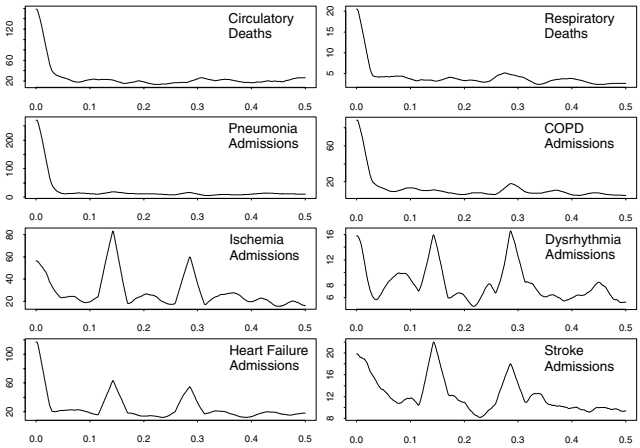

Figure 12. Power spectra of respiratory and circulatory series. Y-axis is the power (variance), X-axis is the frequency (1/day).

be depicted using power spectra (variance breakdown by frequency). Figure 12 shows resulting power spectra for the mortality and hospital admission categories. These spectra depict the relative variance contributions from the seasonal and long-term trends versus day-of-week patterns. Seasonal cycles and other long-wave trends are depicted at a frequency range shorter than about 0.03/day (ie, a period longer than about 1 month). A day-of-week pattern is exhibited at frequencies centered at 0.14/day (7-day cycle) and at 0.28/day (3.5-day cycle) because the pattern is not a pure sinusoid, but a repeating pattern of slow declines during the week and sharp drops on Saturday and Sunday, requiring a higher harmonic of the 7-day cycle. All of the respiratory categories are dominated by seasonal cycles/influenza peaks, whereas the day-of-week pattern contributions are stronger for ischemic heart disease, dysrhythmias, and stroke.

Both seasonal cycles/influenza and day-of-week patterns can cause overdispersion in the hospital admission series when modeled as Poisson series. Seasonal cycles can be fitted using smoothing splines with adequate degrees of freedom. The spectra for the respiratory series suggests the need to control for periodicity of approximately 20 days and longer. We attempted to fit the pneumonia series, the most overdispersed respiratory series, using smoothing splines with equivalent periodicity of 21 days (ie, df = 1,096 days ÷ 21 days ≈ 52) and day-of-week indicator variables in a generalized additive Poisson model. The fitted series as well as the residuals of this model are shown in Figure 13. The strong influenza peak is captured well, leaving essentially no trace of this peak in the residuals.

In the above example, we chose a periodicity of 21 days to control for seasonal cycles and influenza epidemics on the basis of power spectra analyses. Alternatively, we

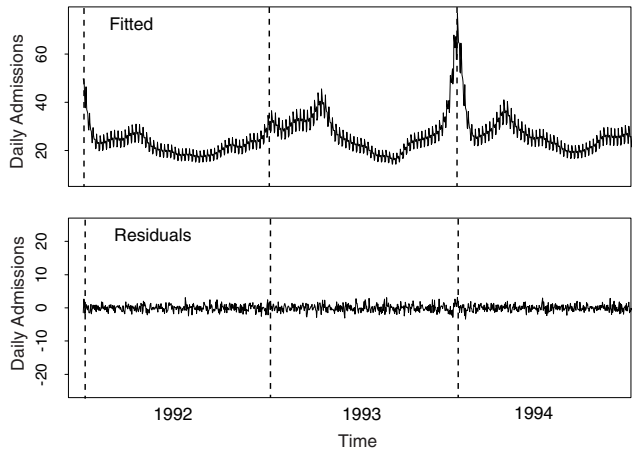

Figure 13. Fitted daily elderly pneumonia hospital admissions and residuals in a generalized additive Poisson model with a smoothing spline with 52 *df* in the three-year period and day-of-week indicator values.

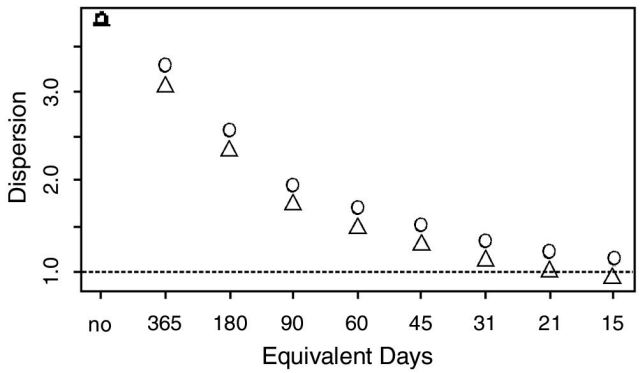

Figure 14. Effects of periodicity to control for seasonal cycles on the residual overdispersion of Poisson regression model. The original series for pneumonia hospital admissions of elderly patients has a strong overdispersion (3.7). An inclusion of smoothing splines with a periodicity of approximately 21 days (open circles) and day-of-week dummy variables (triangles) virtually eliminates the overdispersion.

could have used a priori knowledge that influenza peaks tend to last two weeks or longer. Either way, there remained some ambiguity as to how many days of periodicity could provide an optimal control. Aside from the epidemiologic justification, a statistical aspect of this problem is that such modeling of temporal trends should eliminate overdispersion in the residuals of the Poisson model. One approach to examination of the effect of the choice of degrees of freedom is to actually try a range of periodicity and observe the behavior of the residual overdispersion. The results are plotted over the equivalent moving-average time window (number of observations/*df*). Figure 14 shows the result for the same pneumonia-related hospital admissions series. The overdispersion could be reduced from more than 3.5 (no control) to 1.00 by controlling the periodicity down to approximately 21-day cycles. Note that this periodicity is shorter than that required for the 1985 to 1990 mortality analysis, probably because of the stronger influence and sharper peak of influenza epidemics. Thus, we are fairly confident that smoothing splines can control for even a strong influence of influenza epidemics.

As previously shown, the influence of seasonal cycles and influenza epidemics on hospital admissions for respiratory illness could be adequately controlled using smoothing splines with an equivalent periodicity of approximately 21 days. With these smoothing splines and day-of-week indicator variables in the Poisson model, we next examined various temperature and humidity parameters. Our preliminary results indicated that 2-day lagged temperature variables usually were associated most significantly and negatively with mortality series and that same-day temperature variables were associated positively with mortality. These associations were often nonlinear, and therefore we used LOESS smoothing of hospital admissions over temperature at various lagged days.

Our preliminary results also showed that hot (mean temperature ≥ 80°F) and humid (relative humidity ≥ 70%) days were marginally significant. Therefore we specified models with several combinations of these variables. The AIC and dispersion parameter for some of these regression results are shown in Table 12 to illustrate the contribution of each variable. It can be seen that both the AIC and the dispersion parameter suggest model 1 to be the best. However, model 1 does not control for cold temperature effects, which is not reasonable. Model 2 is second best in terms of AIC and dispersion, but we prefer to keep the hot-and-humid indicator even when it's only weakly predictive and not significant ($t \approx 1$). Model 4, with a one-day lagged hot-and-humid indicator is next best, but the coefficient for this variable was negative, which is not consistent with biological plausibility. Thus, we chose model 3 for the subsequent analyses. In other cases we have observed that smaller AICs do not necessarily result in biologically rational models, probably because of correlation among the covariates chosen. These complications illustrate the difference between epidemiologic models and statistically best fit models.

We next introduced pollution variables (lag days 0 through 3, and multiday average thereof) into the Poisson regression with the weather model specification described above. Significant associations often occurred at multiple lags. Therefore, although selecting the most significant single lag would bias the likelihood of finding a positive association by chance, when multiple lags are significant, such a selection can also underestimate the overall (multilag) pollution effects. Because our main interest is a comparison among the effects of PM components, how-

Table 12. Weather Model Specifications and Resulting AIC and Dispersion Parameter for Pneumonia Admissions (Spline-Smoothed Seasonal Cycles and Day of the Week Included)

Model Number	Model Specification	AIC	Dispersion
1	LOESS of same-day temperature	1141.06	1.019
2	LOESS of same-day temperature + 2-day lagged temperature	1145.28	1.024
3	2 + hot-and-humid indicator	1147.58	1.026
4	2 + 1-day lagged hot-and-humid indicator	1145.59	1.023
5	LOESS of same-day temperature + average of past three days' temperature	1150.12	1.028
6	5 + hot-and-humid indicator	1152.36	1.029
7	LOESS of same-day humidity	1167.73	1.044
8	LOESS of 1-day-lagged humidity	1164.74	1.042
9	2 + 7	1147.18	1.025
10	2 + 8	1147.39	1.026

ever, we selected this approach for reporting results for the most significant lags among 0-day to 3-day lags.

The lag at which the most significant association was observed varied among the pollutants somewhat, but the pattern of lag structures for the PM components was more internally consistent than the pattern of lag structures for the gaseous pollutants. The estimated relative risks for all the single lags (0–3), as well as for 6 multiday lags (ie, 0–1, 1–2, 2–3, 0–1–2, 1–2–3, and 0–1–2–3 lag day averages) are presented in Appendix D. It was apparent that the stronger the associations were with outcomes, the more defined were the distributed lag structures. The effect of using a multiday average lag is that, if distributed positive coefficients are observed in single-day lag results, the multiday lag result (per 5th to 95th percentile increment of the multiday average index) tends to result in a similar effect size. If coefficients are spiky (ie, some positive and some negative or zero) in a single-day lag result, then the estimated effect size in a multiday result is smaller and less significant, as expected.

Again, for the main question of the relative importance of PM components, the most significant single-day lag for each pollutant is shown in Tables 13 and 14. Note that the PM component lags, which often were consistent among the PM components, were different depending on the health outcomes. For example, the 1-day lag was most consistently selected for pneumonia admissions, whereas it was the 3-day lag for COPD admissions, and the 2-day lag for ischemic heart disease.

Figures 15 and 16 show the relative risk per 5th to 95th percentile increment of each pollutant (ie, single-pollutant model) that exhibited the most significant coefficients. Note that, in several of the outcomes, the 95% confidence bands are so wide that even the relatively large relative risks (RR > 1.05) are not significant. This is, in part, because we restricted the data analysis to the study period when H^+ and SO_4^{2-} measurements were available. When we examined the PM mass indices only, without the restriction, they were significant for total mortality, circulatory mortality, COPD, and ischemic heart disease admissions, without notable difference in the effect-size estimates. In general, the effect-size estimates among $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} were comparable and larger than those for H^+ or SO_4^{2-}. Gaseous pollutants, especially O_3, were associated positively with both mortality and admissions.

We next considered two-pollutant models, using each of the PM indices with each of the gaseous pollutants, in each case employing the most significant lag selected in the single-pollutant models (Tables 13 and 14). For total mortality, simultaneous inclusion of O_3 substantially reduced the PM coefficients, whereas for mortality from circulatory causes and hospital admissions for COPD, CO substantially reduced the PM coefficients. In several cases, addition of gaseous pollutants increased the PM coefficients (eg, CO in the case of mortality from respiratory illness).

Because $PM_{2.5}$ and $PM_{10-2.5}$ were complementary size-fractionated components of PM_{10} and only moderately correlated in this data set, we also considered the simultaneous inclusion of these PM mass indices in regression models. In this analysis, we did not restrict the data to the period in which H^+ and SO_4^{2-} were sampled. The results are shown in Figure 17. In most cases, the coefficients for both $PM_{2.5}$ and $PM_{10-2.5}$ were reduced.

Table 13. Mortality and Relative Risks (95% CI) for PM Indices

Pollutant	PM Alone	With O_3 (Lag 0)	With SO_2 (Lag 3)	With NO_2 (Lag 1)	With CO (Lag 1)
Total Mortality					
$PM_{2.5}$ (lag 3)	1.045 (0.991–1.102)	1.041 (0.981–1.106)	1.056 (0.995–1.122)	1.045 (0.990–1.102)	1.044 (0.990–1.101)
$PM_{10–2.5}$ (lag 1)	1.038 (0.988–1.090)	1.030 (0.973–1.090)	1.039 (0.989–1.091)	1.038 (0.985–1.093)	1.036 (0.985–1.089)
PM_{10} (lag 1)	1.044 (0.989–1.102)	1.025 (0.961–1.094)	1.043 (0.989–1.101)	1.050 (0.986–1.118)	1.043 (0.983–1.106)
H^+ (lag 1)	1.010 (0.985–1.036)	1.002 (0.976–1.029)	1.010 (0.985–1.036)	1.009 (0.984–1.035)	1.008 (0.983–1.034)
SO_4^{2-} (lag 1)	1.024 (0.981–1.069)	1.010 (0.964–1.058)	1.022 (0.979–1.067)	1.022 (0.976–1.070)	1.018 (0.974–1.065)
Circulatory Mortality					
$PM_{2.5}$ (lag 1)	1.046 (0.967–1.131)	1.050 (0.958–1.151)	1.075 (0.984–1.175)	1.028 (0.940–1.124)	1.016 (0.932–1.106)
$PM_{10–2.5}$ (lag 1)	1.075 (1.000–1.155)	1.077 (0.990–1.171)	1.081 (1.005–1.164)	1.065 (0.986–1.150)	1.060 (0.984–1.142)
PM_{10} (lag 1)	1.070 (0.987–1.160)	1.075 (0.977–1.184)	1.102 (1.007–1.205)	1.057 (0.962–1.162)	1.042 (0.953–1.138)
H^+ (lag 0)	1.015 (0.978–1.054)	1.017 (0.976–1.061)	1.015 (0.977–1.054)	1.010 (0.972–1.050)	1.006 (0.968–1.047)
SO_4^{2-} (lag 0)	1.018 (0.955–1.085)	1.013 (0.939–1.094)	1.017 (0.952–1.087)	1.006 (0.941–1.076)	1.000 (0.934–1.069)
Respiratory Mortality					
$PM_{2.5}$ (lag 0)	1.033 (0.855–1.248)	0.982 (0.764–1.261)	0.998 (0.804–1.238)	1.062 (0.858–1.315)	1.029 (0.852–1.242)
$PM_{10–2.5}$ (lag 2)	1.071 (0.913–1.257)	0.998 (0.821–1.213)	1.081 (0.920–1.269)	1.077 (0.917–1.265)	1.078 (0.917–1.267)
PM_{10} (lag 0)	1.080 (0.896–1.301)	1.052 (0.822–1.347)	1.059 (0.864–1.299)	1.134 (0.915–1.406)	1.082 (0.898–1.303)
H^+ (lag 1)	1.028 (0.938–1.128)	1.032 (0.938–1.135)	1.029 (0.938–1.129)	1.030 (0.939–1.129)	1.027 (0.936–1.126)
SO_4^{2-} (lag 3)	1.066 (0.908–1.251)	0.985 (0.828–1.172)	0.977 (0.829–1.152)	0.975 (0.827–1.149)	0.977 (0.823–1.161)

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Table 14. Hospital Admissions and Relative Risks (95% CI) for PM Indices

Pollutant	PM Alone	With O_3 (Lag 3)	With SO_2 (Lag 3)	With NO_2 (Lag 3)	With CO (Lag 3)
Pneumonia					
$PM_{2.5}$ (lag 1)	1.185 (1.054–1.332)	1.175 (1.026–1.345)	1.183 (1.052–1.331)	1.186 (1.054–1.335)	1.179 (1.047–1.327)
$PM_{10–2.5}$ (lag 1)	1.114 (1.006–1.233)	1.133 (1.000–1.284)	1.116 (1.008–1.235)	1.114 (1.007–1.234)	1.116 (1.009–1.236)
PM_{10} (lag 1)	1.219 (1.084–1.372)	1.248 (1.082–1.440)	1.219 (1.083–1.371)	1.220 (1.084–1.373)	1.216 (1.081–1.369)
H^+ (lag 3)	1.060 (1.005–1.118)	1.056 (0.995–1.120)	1.062 (1.006–1.122)	1.059 (1.004–1.117)	1.060 (1.005–1.118)
SO_4^{2-} (lag 1)	1.156 (1.050–1.273)	1.135 (1.027–1.255)	1.157 (1.051–1.274)	1.155 (1.048–1.272)	1.152 (1.045–1.269)
COPD					
$PM_{2.5}$ (lag 3)	1.080 (0.933–1.251)	1.040 (0.877–1.234)	1.063 (0.899–1.258)	1.125 (0.951–1.331)	1.079 (0.932–1.249)
$PM_{10–2.5}$ (lag 3)	1.089 (0.960–1.236)	1.003 (0.862–1.168)	1.082 (0.952–1.230)	1.104 (0.965–1.263)	1.093 (0.963–1.242)
PM_{10} (lag 3)	1.098 (0.946 1.274)	1.010 (0.847 1.205)	1.084 (0.920–1.278)	1.155 (0.970–1.377)	1.100 (0.948–1.276)
H^+ (lag 3)	1.067 (1.000–1.138)	1.066 (0.997–1.139)	1.072 (1.003–1.146)	1.073 (1.006–1.146)	1.067 (1.000–1.138)
SO_4^{2-} (lag 3)	1.060 (0.938–1.198)	1.055 (0.928–1.199)	1.078 (0.941–1.235)	1.100 (0.965–1.254)	1.060 (0.938–1.198)

(Table continues next page)

Table 14 (*continued*). Hospital Admissions and Relative Risks (95% CI) for PM Indices

Pollutant	PM Alone	With O_3 (Lag 3)	With SO_2 (Lag 3)	With NO_2 (Lag 3)	With CO (Lag 3)
Ischemic Heart Disease					
$PM_{2.5}$ (lag 2)	1.063 (0.980–1.153)	1.041 (0.947–1.144)	1.062 (0.979–1.152)	1.076 (0.990–1.169)	1.054 (0.965–1.151)
$PM_{10-2.5}$ (lag 2)	1.101 (1.026–1.181)	1.122 (1.030–1.223)	1.102 (1.027–1.182)	1.107 (1.031–1.188)	1.097 (1.021–1.178)
PM_{10} (lag 2)	1.091 (1.005–1.184)	1.085 (0.982–1.200)	1.091 (1.005–1.184)	1.106 (1.017–1.202)	1.087 (0.995–1.187)
H^+ (lag 2)	1.027 (0.991–1.065)	1.024 (0.986–1.063)	1.026 (0.990–1.064)	1.027 (0.991–1.065)	1.027 (0.990–1.065)
SO_4^{2-} (lag 2)	1.026 (0.961–1.095)	1.001 (0.934–1.074)	1.023 (0.958–1.092)	1.026 (0.960–1.096)	1.023 (0.956–1.095)
Dysrhythmias					
$PM_{2.5}$ (lag 1)	1.047 (0.907–1.208)	1.080 (0.904–1.291)	1.034 (0.895–1.194)	1.017 (0.878–1.178)	1.008 (0.863–1.177)
$PM_{10-2.5}$ (lag 0)	1.002 (0.882–1.138)	0.956 (0.817–1.119)	0.999 (0.879–1.136)	0.984 (0.861–1.124)	0.990 (0.871–1.125)
PM_{10} (lag 1)	1.030 (0.891–1.192)	1.047 (0.868–1.262)	1.023 (0.884–1.184)	0.999 (0.860–1.160)	0.987 (0.842–1.157)
H^+ (lag 0)	1.043 (0.974–1.117)	1.057 (0.985–1.134)	1.039 (0.967–1.116)	1.034 (0.964–1.109)	1.028 (0.957–1.104)
SO_4^{2-} (lag 1)	1.032 (0.921–1.157)	1.004 (0.876–1.151)	1.018 (0.908–1.142)	1.010 (0.900–1.133)	1.002 (0.890–1.128)
Heart Failure					
$PM_{2.5}$ (lag 1)	1.133 (1.034–1.241)	1.183 (1.053–1.329)	1.126 (1.028–1.233)	1.127 (1.028–1.235)	1.131 (1.032–1.240)
$PM_{10-2.5}$ (lag 0)	1.050 (0.968–1.138)	1.059 (0.956–1.173)	1.055 (0.974–1.144)	1.051 (0.969–1.139)	1.037 (0.955–1.126)
PM_{10} (lag 0)	1.099 (1.002–1.206)	1.111 (0.989–1.248)	1.101 (1.004–1.208)	1.103 (1.005–1.210)	1.077 (0.974–1.191)
H^+ (lag 0)	1.039 (0.992–1.088)	1.032 (0.983–1.083)	1.038 (0.991–1.087)	1.039 (0.992–1.088)	1.036 (0.989–1.086)
SO_4^{2-} (lag 0)	1.091 (1.012–1.176)	1.080 (0.997–1.170)	1.086 (1.008–1.171)	1.089 (1.010–1.174)	1.088 (1.007–1.177)
Stroke					
$PM_{2.5}$ (lag 0)	1.026 (0.925–1.139)	0.986 (0.877–1.109)	1.029 (0.927–1.142)	1.027 (0.912–1.157)	1.011 (0.902–1.132)
$PM_{10-2.5}$ (lag 1)	1.047 (0.955–1.148)	1.028 (0.919–1.150)	1.049 (0.956–1.150)	1.041 (0.949–1.143)	1.046 (0.955–1.147)
PM_{10} (lag 1)	1.049 (0.944–1.165)	1.068 (0.942–1.210)	1.049 (0.944–1.165)	1.041 (0.934–1.160)	1.046 (0.942–1.163)
H^+ (lag 1)	1.024 (0.977–1.074)	1.022 (0.973–1.072)	1.025 (0.977–1.075)	1.025 (0.977–1.074)	1.024 (0.977–1.074)
SO_4^{2-} (lag 1)	1.015 (0.934–1.104)	1.017 (0.932–1.110)	1.017 (0.935–1.106)	1.016 (0.933–1.106)	1.014 (0.933–1.103)

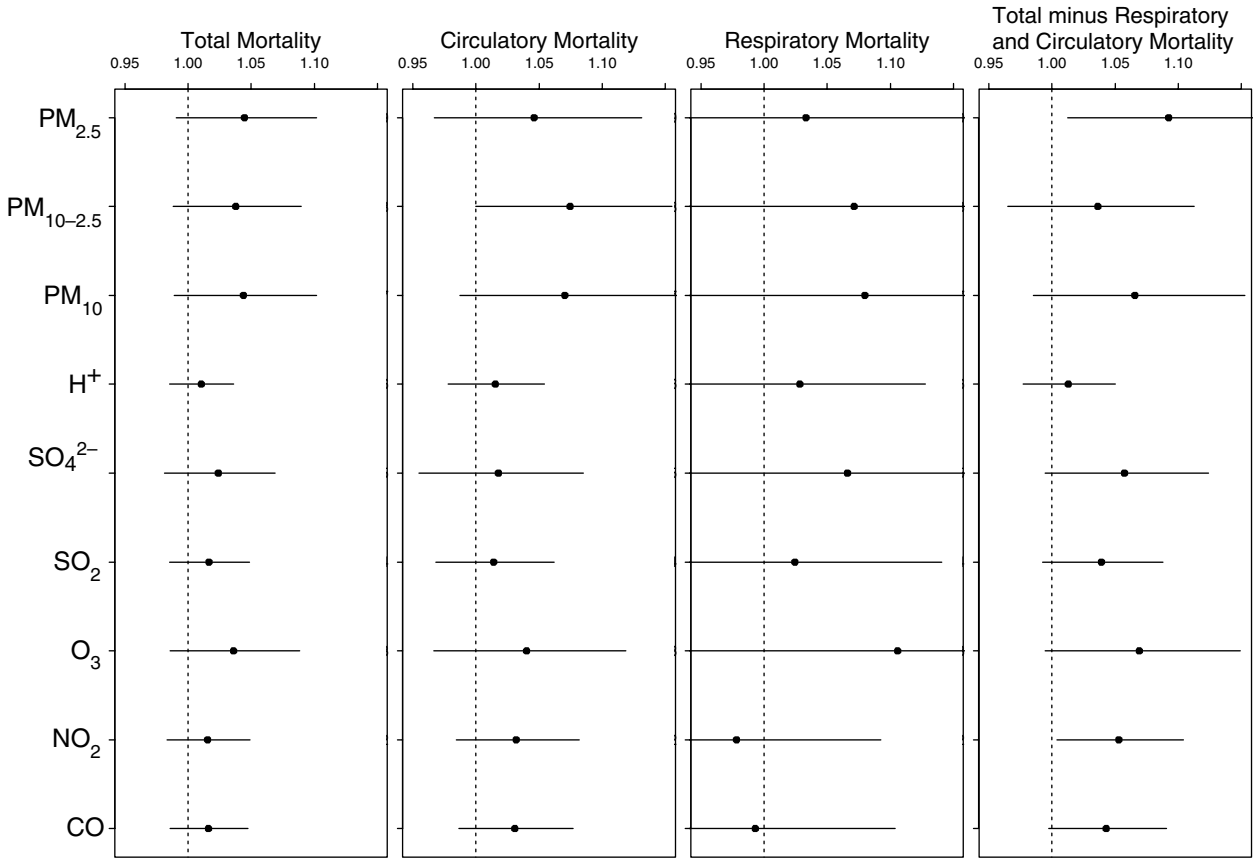

Figure 15. Mortality outcomes. Relative risks per 5th to 95th percentile pollution increment.

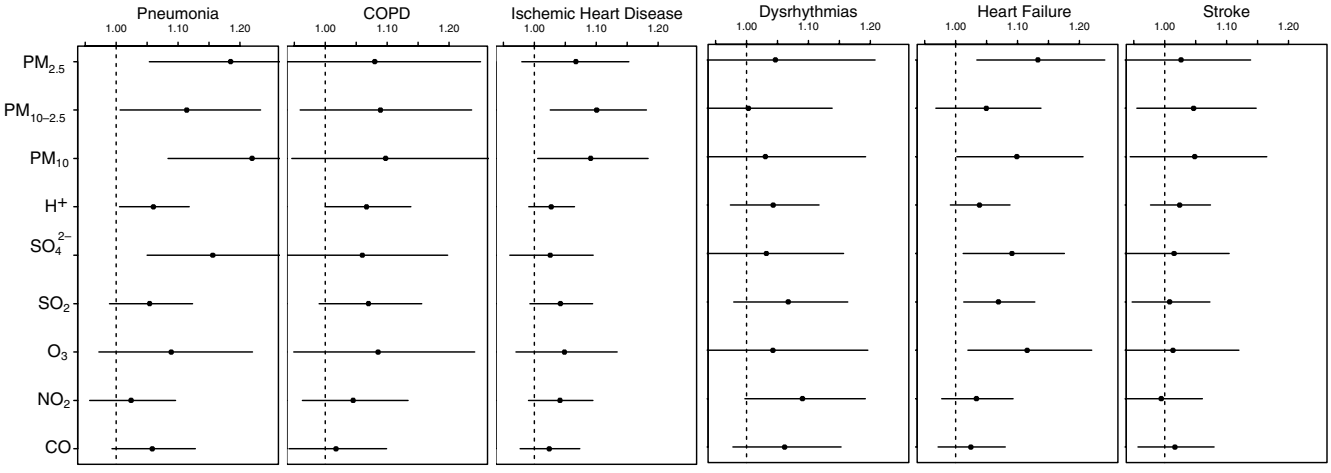

Figure 16. Elderly hospital admission outcomes. Relative risks per 5th to 95th percentile pollution increment.

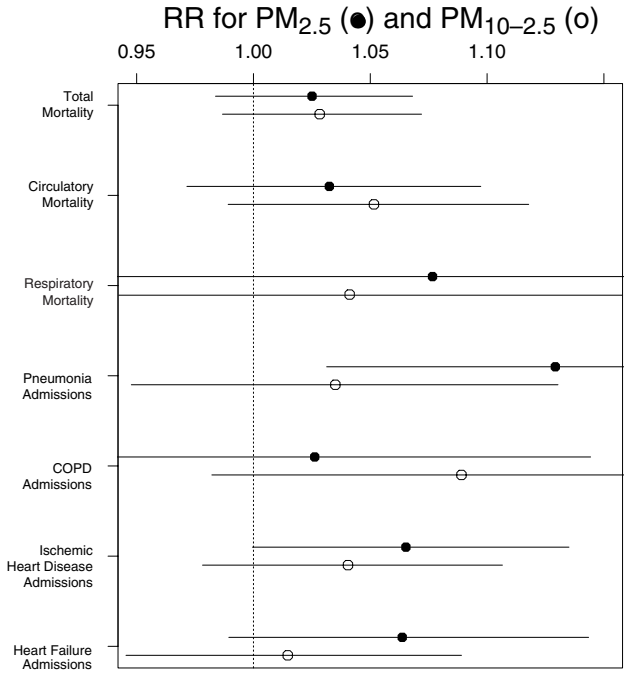

Figure 17. Relative risks per 5th to 95th percentile increment of $PM_{2.5}$ and $PM_{10-2.5}$ simultaneously included in Poisson regressions. Data were adjusted for seasonal cycles, temperature (LOESS of same day and LOESS of average of 1 to 3 lags, and hot and humid indicator), and day of the week.

DISCUSSION

BEST PREDICTORS OF PM COMPONENTS

These results indicated that (1) in the 1985 to 1990 mortality analysis, the mortality relative risk estimates and their significance were generally, in descending order of magnitude, PM_{10}, TSP, TSP–SO_4^{2-}, and TSP–PM_{10}; and (2) in the 1992 to 1994 data analyses, the estimated relative risks per the equivalent distributional increment were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for mortality and hospital admission categories; H^+ and SO_4^{2-} were less associated with the health outcomes examined than were the PM mass indices, and when they were associated with health outcomes, SO_4^{2-} associations were stronger than those for H^+. Collectively, these results do not support our study hypothesis that the strength of association among PM components and health outcomes is, in descending order of magnitude, H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, and TSP.

An interpretation of these results requires some caution because, although the names of these PM mass indices may suggest some distinct separation in size range, the data suggest that the mass of the smaller size index could explain a substantial fraction of the variation in the larger PM size index. For example, in these data, $PM_{2.5}$ accounted for, on average, 60% of PM_{10} (and up to 80% on some days); and PM_{10}, on average, accounted for 66% of TSP mass. The temporal correlation between TSP and PM_{10} was moderate ($r = 0.63$), but the temporal correlation between $PM_{2.5}$ and PM_{10} was high (0.9). Thus, the apparent associations between the larger-size PM indices and health outcomes may be driven by the smaller particles. The fact that TSP–PM_{10} was not associated with mortality in the 1985 to 1990 analysis also suggests that the largest particles (ie, 10 to 50 μm in diameter) were not responsible for the observed associations between TSP and mortality, as expected in our hypothesis. However, in the 1992 to 1994 analysis, $PM_{10-2.5}$ did show effect-size estimates that are comparable to (or sometimes even higher than) those for $PM_{2.5}$. Because $PM_{10-2.5}$ and $PM_{2.5}$ were not highly correlated, possibly the observed associations between coarse particles and health outcomes were not confounded by smaller particles.

Some limitations in the available data set prevent simple interpretations. The acidity levels were very low and, on the majority of study days, they were below the detection limit. Also, the TSP–SO_4^{2-} data have added measurement error due to artifactual formation of SO_4^{2-} on the TSP glass-fiber filter. Despite these caveats, the results obtained do suggest that, among the PM components examined, acidity was not a good predictor of health outcomes. These results also suggest that PM components other than H^+ can be harmful.

COMPARISONS WITH PAST STUDIES

Several past studies have examined mortality or morbidity effects of air pollution in Detroit; therefore, we first compare our results to these Detroit data analyses. Schwartz (1991) reported an association between TSP and nonaccidental mortality in the city of Detroit during 1973 to 1982. The missing TSP values (5 out of 6 days) were filled in via regression of TSP on humidity-corrected extinction coefficients (derived from daytime airport visual range). Schwartz reported that SO_2 was also a significant predictor in a single-pollutant model, but in the model with TSP, the SO_2 coefficient became insignificant. Ozone was "highly insignificant" as a predictor of daily mortality in his study. In our results, TSP was a significant predictor, but so was O_3. Sulfur dioxide in our analysis was associated less significantly with mortality, and simultaneous inclusion of SO_2 and each of the PM indices did not change the PM coefficients. The estimated excess death rate per 100 μg/m^3 of TSP in the Schwartz study was 6%, larger than the 2.4% in our study. The most significant lag for TSP was the same (1-day lag) in both studies. In our study, PM_{10} gave relative risks somewhat larger and more

significant, or comparable to those for TSP for the same distributional increment. Because H^+ particles are more efficient in scattering visible light and reducing visual range than are other components of TSP, the TSP data imputed with visual range in the Schwartz study actually may have fit TSP to SO_4^{2-} fine particles.

Schwartz (1994) analyzed the data on hospital admissions of elderly patients for pneumonia, COPD, and asthma in relation to air pollution (PM_{10} and O_3 only) for the Detroit MSA during the period 1986 to 1989. After adjustments were made for temperature, dewpoint, and temporal trends, both PM_{10} and O_3 were associated with pneumonia and COPD, but not with asthma admissions; and, when both pollutants were included, both remained significant predictors.

In our analysis, in the case of pneumonia, O_3 coefficients were positive but not significant, whereas all the PM coefficients were significantly positive. Also, when O_3 and $PM_{2.5}$ were considered simultaneously, $PM_{2.5}$ remained significant and its coefficient was reduced only slightly. In our results for COPD, O_3 and $PM_{2.5}$ exhibited similar relative risks for the same distribution increment with comparable significance levels, but in a two-pollutant model, the $PM_{2.5}$ coefficient decreased substantially. Thus, in our data, some extent of confounding between the effects of O_3 and PM was possible.

Schwartz and Morris (1995) analyzed the data on hospital admissions of elderly patients in the Detroit MSA. Admissions for ischemic heart disease, dysrhythmias, and heart failure were examined in relation to air pollution for the period 1986 to 1989. After adjustments were made for temperature, dewpoint, and temporal trends, PM_{10} was associated with ischemic heart disease ("SO_2, CO, and O_3 made no independent contributions…"); both PM_{10} and CO showed "independent associations" with admissions for heart failure; and no pollutant was associated significantly with dysrhythmias.

In our analysis, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ showed larger effect-size estimates with ischemic heart disease than did other pollutants (which also were associated positively), but the simultaneous consideration of O_3 and $PM_{2.5}$ reduced the $PM_{2.5}$ coefficient. Heart failure was associated with all the PM components, as well as with O_3. Also in our analysis, admissions for dysrhythmias were associated positively but not significantly with most pollutants. Dysrhythmia admissions have the smallest daily mean counts among the health outcomes examined; therefore, it is not surprising that these associations were not significant in an analysis based on the short study period.

Morris and colleagues (1995) analyzed associations between gaseous air pollution (PM indices not considered) and hospital admissions for heart failure in 7 large US cities, including Detroit, between 1986 and 1989. Their major finding was that, after adjusting for temperature, seasonal trends, and day of the week, CO was associated most consistently with admissions for heart failure across cities, including Detroit. In their analysis, none of the other gaseous pollutants were associated with admissions for heart failure.

In our analysis, $PM_{2.5}$ was associated most significantly with heart failure, but O_3 and SO_2 also were associated significantly, with larger effect-size estimates than those for NO_2 and CO (which were not associated significantly). The PM coefficients in our analysis were not reduced when each of the gaseous pollutants was included in the regression model simultaneously.

Thus, when compared to other Detroit studies, our results show some consistencies in terms of PM associations with health outcomes, but some inconsistencies regarding O_3 and CO associations. In our study, O_3 was associated with heart failure (which it had not been, in other studies). The relatively small sample size of our study made it difficult to separate out individual associations between pollutants and health outcomes, but we did not observe a consistent pattern to suggest CO effects in cardiac outcomes.

We also were interested in comparing our results to those from studies in other cities that investigated the effects of PM components and gaseous pollutants. As mentioned, a series of studies were conducted in Ontario, Canada, and the northeastern US (eg, Bates and Sizto 1983, 1987; Thurston et al 1992, 1994; Burnett et al 1994, 1997a,c; Delfino et al 1994) that investigated the effects of summer haze air pollution. These studies collectively suggest that summer haze constituents, especially O_3 and SO_4^{2-}, were associated with respiratory hospital admissions. Some of these studies analyzed the PM components that our study examined, and therefore are discussed here.

Thurston and associates (1992) analyzed H^+, SO_4^{2-}, and O_3 in relation to hospital admissions (all ages) for major respiratory problems and asthma in four New York State metropolitan areas (Buffalo, Albany, White Plains, and New York City) for the summers of 1988 and 1989. Adjusted for time trends, day of the week, and temperature, H^+, SO_4^{2-}, and O_3 were all significant predictors of total respiratory and asthma-related admissions in Buffalo and New York City (associations were weaker in Albany and White Plains). Gwynn and coworkers (1999) did a follow-up to this study using the extended data set (1988 to 1990 year-round) for Buffalo, adding mortality data and also considering coefficient of haze (COH), CO, SO_2, and NO_2. They reported that H^+ and SO_4^{2-} showed "the most

coherent associations" across both respiratory hospital admissions and mortality.

In our analysis, H^+ and SO_4^{2-} were not significant predictors of any of the three mortality series examined (total, circulatory, and respiratory). Acidity and SO_4^{2-} were significant predictors for pneumonia admissions among elderly patients, but not for COPD admissions. The most notable difference between our Detroit data and the New York State data is in the H^+ levels: in the study by Thurston and associates, the average summer H^+ levels for 1988 and 1989 ranged from 45 to 67 nmol/m^3; in the study by Gwynn and coworkers, the average H^+ level was 36.4 nmol/m^3; in our study, the average H^+ level was 8.8 nmol/m^3. Thus, the H^+ levels in our Detroit data set were much lower than those in the New York State data set.

Thurston and colleagues (1994) also examined the relations among several PM components (H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10}, and TSP), O_3, SO_2, NO_2 and hospital admissions for respiratory illness in Toronto, Ontario, during the summers of 1986, 1987, and 1988. After adjustment for longwave temporal trend and temperature, only the O_3, H^+, and SO_4^{2-} associations with respiratory and asthma admissions remained consistently significant. The relative particle metric strengths of associations with admissions were generally, in descending order of magnitude, H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10}, and TSP, "indicating that particle size and composition are of central importance in defining the adverse human health effects of particulate matter," the authors concluded.

By contrast, in our analysis H^+ and SO_4^{2-} did not show stronger associations than PM_{10} or $PM_{2.5}$, and when H^+ and SO_4^{2-} were both significant predictors of hospital admissions (for pneumonia and heart failure), SO_4^{2-} was associated more significantly than H^+. Again, a notable difference between the data of Thurston and colleagues from Toronto and our data is the H^+ levels: the H^+ levels in Toronto were 21.4, 12.6, and 52.3 nmol/m^3 for the summers of 1986, 1987, and 1988, respectively, whereas in our study, the H^+ level averaged only 8.8 nmol/m^3.

Burnett and coworkers published a series of studies based on data from Canada, investigating: (1) O_3, SO_4^{2-} and hospital admissions for respiratory illness in Ontario, 1983 to 1988 (1994); (2) SO_4^{2-} and cardiac and respiratory admissions in Ontario, 1983 to 1988 (1995); (3) O_3 and respiratory admissions in 16 Canadian cities, 1981 to 1991 (1997a); (4) CO and hospital admissions for congestive heart failure in elderly patients in 10 Canadian cities, 1981 to 1991 (1997c); (5) PM components (and gaseous pollutants) and respiratory and cardiac hospital admissions in Toronto, Ontario, 1992 to 1994 (1997b); (6) CO and daily mortality in Toronto, Ontario, 1980 to 1994 (1998b); (7) the effects of urban gaseous air pollution mix on mortality in 11 Canadian cities (1998a); and (8) size-fractionated PM and gaseous pollutants and cardiac and respiratory hospital admissions in Toronto, Ontario, 1980 to 1994 (1999). Because of our specific interest in PM components, we compared studies (5), (7), and (8) to our results.

Because our PM components data in Windsor came from the Canadian PM components sampling network, our study examined an array of air pollutants essentially identical to those analyzed in the study by Burnett and colleagues (1997b) in Toronto, Ontario, 1992 to 1994 (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4^{2-}, H^+, O_3, NO_2, SO_2, and CO), except that we did not include COH. Both studies examined hospital admissions related to respiratory and cardiac diseases, but the study by Burnett and coworkers used admissions of patients of all ages, whereas our study used hospital admissions of elderly (age 65 and over) patients only. Also, Burnett and coworkers differentiated between the total respiratory and total cardiac categories, whereas we performed separate analyses for each respiratory and cardiac admission category. Particulate matter component levels in Toronto and Detroit were comparable: PM_{10} levels were 28 versus 31 μg/m^3; $PM_{2.5}$, 17 versus 18 μg/m^3; H^+, 5.0 versus 8.8 nmol/m^3; and SO_4^{2-}, 57 versus 54 nmol/m^3. Although a direct comparison between the two cities of gaseous levels was not possible (our study used a daily 24-hour average, and Burnett and coworkers presented daily 1-hour maxima), a comparison of our data with the distribution of daily average values published in another Toronto study (Burnett et al 1999) suggests that the gaseous pollution levels also were comparable for these two cities, with the exception of CO, which was higher in Toronto (1.18 ppm) than in Detroit (0.72 ppm). In the analysis by Burnett and colleagues, after adjustment for weather and seasonal cycles, the strongest associations with both respiratory and cardiac diseases were observed for COH and O_3. In single-pollutant models, essentially all the pollutants were associated with the respiratory or cardiac hospital admissions, but in models with three gaseous pollutants, O_3, NO_2, and SO_2, and 1 PM component, only COH remained significant. Burnett and associates concluded that "PM mass and chemistry could not be identified as an independent risk factor for the exacerbation of cardiorespiratory diseases in this study beyond those attributable to climate and gaseous air pollution." In our study, by contrast, gaseous pollutants generally were not correlated as strongly with health outcomes as PM was, especially in its mass components. Ozone, in our analysis, was significantly associated with heart failure. Most of the pollutants were associated positively with COPD (although not significantly); when O_3 was simultaneously included in

regression with PM mass indices, their coefficients were substantially reduced, again suggesting some sharing of the effects.

The basic difference between the Toronto study and our Detroit study is that in the Toronto data essentially all the pollutants were associated with hospital admissions, and multiple-pollutant models with three gaseous pollutants eliminated PM effects, except in the case of COH; whereas in our study, although gaseous pollutants also were associated with health outcomes, simultaneous inclusions of PM indices and gaseous pollutants did not eliminate PM associations. It should be noted that, in the study by Burnett and associates (1997b), there was no consistent pattern to suggest a significance ranking among PM constituents in associations with hospital admissions, except that COH was always the most significant predictor of all the hospital admissions. However, in that study, in one- and two-pollutant models most of the PM indices were significant for respiratory admissions.

In a separate factor analysis of earlier Toronto data by Özkaynak and associates (1996), a factor with large loadings on COH, as well as on NO_2 and CO, was considered to be an automobile traffic factor (this identification was based on a review of source emissions). On the other hand, TSP was not highly loaded on the automobile traffic factor but rather, on a factor of its own. Coefficient of haze, which is a measure of elemental carbon, was considered as a reasonable surrogate for motor vehicle emissions. Thus, it is possible that, in Toronto, automobile-related PM had a more important role in health effects than did secondary aerosols.

Burnett and associates (1998a) analyzed the effects of gaseous pollutants on daily mortality in 11 Canadian cities. They found that the estimated impact on mortality was largest for NO_2, followed by O_3, SO_2, and CO, respectively. Although no PM indices were analyzed in that study, Burnett and associates estimated that, on the basis of $PM_{2.5}$ results from other cities, the impact of these gaseous pollutants was greater than that for $PM_{2.5}$. It is interesting to note, however, that the city-specific results showed that the associations of gaseous pollutants with health outcomes were far less significant in Windsor than in Toronto. This is to some extent consistent with our Detroit results, in which gaseous pollutants generally were not associated more significantly with the health outcomes examined.

Burnett and associates (1999) further analyzed Toronto data for the period 1980 to 1994 to investigate the association of PM and gaseous pollutants with cardiorespiratory hospital admissions. The admission data were analyzed individually for the following categories: asthma, COPD (excluding asthma), respiratory infection, dysrhythmias, heart failure, ischemic heart disease, cerebral vascular diseases, and diseases of peripheral circulation. Age stratification was not considered. Carbon monoxide, NO_2, SO_2, O_3, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were considered; the missing values in the size-fractionated PM data were filled in on the basis of the relation between the actual size-fractionated PM (measured every sixth day) and TSP, TSP–SO_4^{2-}, and COH. Air pollution was associated only weakly with cerebral vascular (ie, stroke) and peripheral vascular diseases. Both (the estimated) $PM_{2.5}$ and $PM_{10-2.5}$, as well as PM_{10}, were associated with the rest of the admission categories, but their estimated effects were reduced when gaseous pollutants were considered simultaneously. These reductions ranged from 30% (COPD) to 80% (heart failure) for $PM_{2.5}$, 28% (asthma) to 100% (ischemic heart disease) for $PM_{10-2.5}$, and 33% (COPD) to 100% (ischemic heart disease) for PM_{10}. In our analysis, simultaneous consideration of O_3 also reduced $PM_{2.5}$ coefficients when O_3 by itself was associated with the outcome (ie, 75% for COPD, and 54% for ischemic heart disease). Thus, at least some of the observed PM effects are confounded by the influence of other gaseous pollutants. In terms of the consistency of hospital admission categories that were associated with air pollutants, both the study by Burnett and coworkers and our results showed associations between PM indices and COPD, respiratory infection (≈ pneumonia in our study), heart failure, and ischemic heart disease. Our analysis did not show an association between air pollution and dysrhythmias, whereas the analysis by Burnett and coworkers did. In neither of these studies was stroke (≈ cerebral vascular disease in Burnett) associated with air pollution, although this may be due in part to this category's smaller daily counts.

Analyses by Thurston and colleagues (1992, 1994) of summer data from Toronto (1986 to 1988) and New York (1988 to 1989) contrast with studies by Burnett and coworkers (1997b, 1999). With the exception of O_3, the association of gaseous pollutants with hospital admissions was generally weaker in the analysis of Thurston and colleagues. Further, Burnett and coworkers did not observe an association between admissions and relative particle strength (in descending order of magnitude, H^+, SO_4^{2-}, $PM_{2.5}$, and PM_{10}). The H^+ levels in the study by Thurston and associates during the summers of 1986 to 1988 also were considerably higher than the H^+ levels in the 1992 to 1994 summer data of Burnett and coworkers. There are, however, some similarities between the the two analyses. All the PM indices (except TSP–PM_{10} in the analysis of Thurston and associates) were associated with hospital admissions in respiratory categories, and the simultaneous

consideration of O_3 reduced PM coefficients, although in most cases PM indices remained significant. In the analysis of Burnett and coworkers, additional inclusions of other gaseous pollutants in regression often reduced the PM coefficients further.

Schwartz and colleagues (1996) investigated the relative strength of associations between PM components and mortality using the Harvard Six Cities data for years 1979 to 1988. Components considered were PM_{10}, $PM_{2.5}$, $PM_{10–2.5}$, SO_4^{2-}, and H^+. Gaseous pollutants were not considered. After adjustment for temperature and temporal trends, $PM_{2.5}$, SO_4^{2-}, and PM_{10} each were associated significantly with daily mortality, but $PM_{10–2.5}$ and H^+ were not. The H^+ levels in these cities during the study periods were higher than those in our study (the highest, 36.1 nmol/m^3, was in Harriman; and the lowest, 10.3 nmol/m^3, was in Steubenville; compared to 8.8 nmol/m^3 in our study). It should be noted that the sample size for H^+ in the Six Cities study was substantially smaller (< 20%) than those for other PM indices examined, and the lack of association with H^+ may be due to this small sample size. The only one of the six cities where $PM_{10–2.5}$ was a significant predictor of mortality was Steubenville, where PM levels (mean $PM_{2.5}$ = 29.6 µg/m^3) and the correlation between $PM_{2.5}$ and $PM_{10–2.5}$ (r = 0.69) were higher than those in other cities. The simultaneous inclusion of $PM_{2.5}$ and $PM_{10–2.5}$ in the Six Cities data resulted in unchanged coefficients for $PM_{2.5}$, but essentially zero coefficients for $PM_{10–2.5}$. In our study, both $PM_{2.5}$ and $PM_{10–2.5}$ were associated with mortality series, and the simultaneous consideration of both indices resulted in a reduction in both their coefficients. The correlation between $PM_{2.5}$ and $PM_{10–2.5}$ (r = 0.42) in our study was modest.

There are a number of factors that can cause discrepancies among studies, including differences in sample size, pollution levels, intercorrelation among pollutants, susceptibility of population, variable selection or availability, model specification, and health outcome grouping (eg, age stratification). Despite these factors, we may summarize the results of the studies discussed above as follows:

- PM mass indices generally are associated with mortality and morbidity, and although some studies suggest a greater role of fine particles than coarse particles, the relative importance has not been implicated consistently;
- H^+ and SO_4^{2-} effects are less consistent among studies, possibly due to differences in their levels or greater exposure measurement errors;
- the coefficients of PM mass indices often remain significant in two-pollutant models, but can be reduced, especially by O_3; and
- gaseous pollutants also are associated with mortality and morbidity outcomes, but cause specificity of associations has not been consistent.

ESTIMATED EFFECT SIZE AND SAMPLE SIZE

One of the limitations of this study was the relatively short study period, especially in the 1992 to 1994 analysis. Although Detroit is a relatively large city, examination of specific health outcome subcategories also was difficult due to their smaller daily counts. The shorter study period and smaller daily counts both contributed to the wider confidence bands for the estimated effect sizes. Thus, there was not enough separation between estimates to clearly support one relative ranking over another. In general, however, the estimated effect size was larger for admission categories such as pneumonia and heart failure than for mortality categories. Also, in the 1985 to 1990 analysis, the relative risks were larger for respiratory mortality than for other mortality categories.

One additional complication in assessing the effect-size estimates among different pollution indices is the influence of the skewness in distribution, because we used the same distributional increment to calculate relative risks. This is not a problem when comparing the relative risks estimated for $PM_{2.5,}$ $PM_{10,}$ and $PM_{10–2.5}$ (and TSP) because their distributional shapes are similar. As can be observed for most of the size-fractionated PM results, their relative 95% CIs are comparable per the distributional increment (ie, 5th to 95th percentile increment), such that their relative significance essentially reflects their effect size. In other words, among the size-fractionated PM indices (eg, TSP, $PM_{10,}$ $PM_{10–2.5}$), we are not dealing with a situation in which two PM indices have the same extent of significance and yet have different levels of effect. This is not the case with H^+, however, which has the most skewed concentration distribution. When the relative risk for H^+ is calculated per 5th to 95th percentile increment, its effect size (and confidence bands) appear smaller than those for other pollutants. For SO_4^{2-}, the effect is intermediate. We did not further search for other increments to calculate and compare relative risks among different pollution indices.

POSSIBLE INFLUENCE OF ENVIRONMENTAL MEASUREMENTS CHARACTERIZATION ERROR

An examination of site-to-site temporal correlation (1981 to 1994 data) showed that the ranking of median site-to-site correlation was O_3 (0.83), PM_{10} (0.78), TSP

(0.71), NO_2 (0.70), CO (0.50), and SO_2 (0.49). This ranking can be explained to some extent. O_3 and PM (whose indices include a significant fraction of SO_4^{2-}) are largely secondary pollutants, and therefore tend to be distributed spatially more uniformly within the city than are primary pollutants such as CO and SO_2, whose concentrations are likely strongly influenced by local emission sources. Fine particles, and especially SO_4^{2-}, are expected to show even better site-to-site correlation than PM_{10} or TSP, but unfortunately we did not have multiple monitors for $PM_{2.5}$ or SO_4^{2-} in our database. Wilson and Suh (1997) investigated this issue in St Louis and Philadelphia, and found that site-to-site correlations for $PM_{2.5}$ ($r \sim 0.9$) were higher than those for $PM_{10-2.5}$ ($r \sim 0.4$). However, NO_2, which is not a regional secondary pollutant, also showed a relatively high site-to-site correlation. One possible reason may be a contribution from broadly distributed motor vehicle sources. Thus, spatial uniformity of pollutants may be due to area-wide sources, or to transport (eg, advection) of fairly stable pollutants into the urban area from upwind sources. Relative spatial uniformity of pollutants would therefore vary from city to city or region to region.

If multiple monitoring sites for a given pollutant within a city show very high site-to-site correlations, then one may be assured that, for an epidemiologic study, the choice of a site is not critical for that pollutant. Thus the site-to-site correlation may serve as an index of the lack of environmental measurements characterization. The fact that the pollution indices that showed high site-to-site temporal correlation (ie, O_3, PM_{10}, and TSP) showed more consistently significant mortality associations in this analysis and some others may suggest that a spatially uniform air pollutant may have smaller exposure misclassification errors in this type of analysis. There are, of course, exceptions in which SO_2 or CO was a significant predictor of daily health outcomes (eg, Morris et al 1995; Moolgavkar and Luebeck 1996; Kelsall et al 1997). Because the ranking of the site-to-site correlations among pollutants is expected to vary from region to region, or city to city, depending on the source types and topographical features, this issue will need to be examined city by city. It is also possible that a site that is not correlated with others may in fact affect sensitive subpopulations surrounding the site and contribute to the excess mortality or morbidity.

In the analysis of 14 TSP sites (1981 to 1987), the result suggested that estimated TSP relative risks per a given distributional increment were not sensitive to the choice of site. When the site locations are compared with population density on the map, the relative risk and corresponding population density have no apparent relationship. In fact, the site that showed the highest significance (site w) is located in the least populated area. It is possible that lack of strong local impact helps the site's representativeness for citywide exposure.

Note that site-to-site variability is only one aspect of error in environmental measurements characterization. Person-to-monitor error may explain a substantial fraction of the overall environmental measurements characterization error. For example, the site-to-site temporal correlation of O_3 may be very high, but in a city where air conditioning is prevalent, ambient O_3 may not be a good index of population exposure to O_3 in that city. A study of personal O_3 exposures in southern California (Avol et al 1998) reported that the average indoor/outdoor ratio was 0.37 and that the presence of air conditioning was an important parameter affecting personal O_3 exposure. The person-to-monitor error is also likely different among the weather and pollution variables. Overall assessment of the relative contribution of these errors in environmental measurements characterization will be possible when indoor and personal exposure studies provide such information.

As an additional source of error in possible environmental measurements characterization, we mentioned a possible artifactual formation of SO_4^{2-} (from SO_2) on the TSP glass-fiber filter in the 1985 to 1990 data. Artifact sulfate formation on glass-fiber filters was mentioned in the study by Burnett and coworkers (1994) of hospital admissions in Ontario, which cites Dann's (1990) study of colocated high-volume samplers using Teflon and glass-fiber filters during the summer of 1978. Using 24 pairs of measurements, Dann derived a predictive equation: sulfates (Teflon filter) = −2.61 + 0.89 sulfates (glass-fiber filter), $R^2 = 0.95$. On the basis of this equation, the median level of TSP–SO_4^{2-} in our study (10.2 μg/m^3) would be reduced to 6.5 μg/m^3, which is a rather large (57%) bias. Although this information is important evidence of artifactual sulfate formation on glass-fiber filters, it does not help us in figuring out how the temporal signal of artifact-free sulfate was perturbed by variable artifact formation. The temporal error (not the constant or proportional bias) would be caused by day-to-day fluctuations in the conditions that help artifact formation (ie, SO_2 and moisture). Although the high R^2 in the regression in Dann's study suggests that the error was constant and proportional in nature, the study was conducted in only one summer and a long time ago, when SO_2 levels were presumably much higher. Therefore, this equation may not be applicable to 1985 to 1990 period.

Finally, the information needed to fully evaluate the effects of error (analytical, person-to-monitor, monitor-to-monitor, etc) in time-series or longitudinal analysis is the variance of error relative to the variance of the temporal

fluctuations of pollution. Basic characterizations of these errors (eg, concentration dependency, normality, etc) are needed to start to incorporate such information in the health effects analyses.

RELIABILITY AND INTERPRETATION OF OUTCOME MEASURE

Limitations of the use of hospital admission data for epidemiologic studies of air pollution effects have been discussed in the past (Bennett 1981). Although the methodologic issues raised by Bennett (eg, control for seasonal variation, day of the week, autocorrelation) have been addressed in most recent studies, issues related to the quality of the hospital admissions data rarely have been discussed. There have been, however, some studies that investigated the accuracy of diagnoses and procedures by reabstraction of medical records. The Institute of Medicine (1980), in a nationwide sample of the National Hospital Discharge Survey data, found that for overall category, agreement at the 3-digit ICD-9 level was 74.9%. The lowest agreement was found for chronic ischemic heart disease (43.5%). Agreement for respiratory categories was 72.1% overall, but 79.6% for bronchopneumonia. A more recent study (Delfino et al 1993) in Quebec, designed to measure the reliability of discharge diagnoses for air pollution research, reported a similar (75.5%) agreement level for respiratory diagnoses, but reported a high agreement for asthma (94.9%). A reabstraction study to measure the accuracy of Medicare data (Fisher et al 1992) found that agreement increased over the years (overall, 73% in 1977 to 78% in 1985) but varied across diagnostic categories. In the study by Fisher and colleagues, agreement for respiratory categories was somewhat lower (65.8%) than in other studies. High agreement (84.3%) was reported for congestive heart failure. Because the misclassification of diagnosis is unlikely to coincide with daily changes in air pollution, misclassification would only attenuate the associations between air pollution and health outcomes. Furthermore, the likely difference in the reliability across diagnosis category would result in differences in the attenuation. This makes it difficult to interpret the pattern of air pollution associations across diagnostic categories. These studies did not report the reliability measure for each of the diagnosis categories we examined in our study, and therefore we cannot quantitatively evaluate how such difference in reliability affected the relative significance of air pollution association with each outcome.

Another hospital admission data issue raised by Bennett (1981) was the effect of readmissions on the estimated health effects of pollution. He speculated that repeated admissions by a small number of patients could cause "distortions in the data leading to false conclusions." As part of our study, we investigated this issue by constructing separate time series, using pneumonia and COPD, for patients who had only one hospital admission over the study period and for patients who had multiple admissions. For pneumonia, the extent of multiple admissions was not substantial (average admissions per individual of 1.17), and the PM_{10} relative risk estimate for the populations with multiple admissions was comparable. For COPD, the extent of multiple admissions was substantial (average admissions per person = 1.58), and the PM_{10} relative risk estimate for that population was smaller than that for the population with single admissions. These results suggest that the estimated PM relative risks for the entire population were not biased upward by the subgroup with multiple admissions.

Coherence of effects across different health endpoints is one of the criteria suggested by Bates (1992) for evaluating causes of health effects related to air pollution. Another question may be whether the effects are sequential. That is, is the patient who is admitted to a hospital because of exposure to air pollution also the one who dies? Such an issue was partly addressed in Schwartz's analysis of Philadelphia data (1994), in which he reported that dead-on-arrival rates were higher for days with high air pollution, (ie, people dying due to elevated air pollution were not dying in a hospital). In our study, we examined the length of stay for patients who died in the hospital after admission for respiratory causes and found that the median length of stay was over a week. Considering that associations between PM and both mortality and hospital admissions in this and other studies lag after exposure by only 1 or 2 days, the majority of those hospitalized due to air pollution are unlikely to be those who die because of that exposure.

Characterization of mortality time series in this data set showed that not only respiratory admissions and respiratory mortality, but also circulatory mortality and total minus circulatory and respiratory mortality, were influenced by influenza epidemics (there were no influenza peaks in hospital admissions for cardiovascular disease). This suggests some overlap or misclassification in underlying causes of deaths between circulatory (or other nonrespiratory causes) and respiratory categories. It is possible that a person with a chronic cardiovascular condition develops an acute respiratory condition, which in turn is aggravated by air pollution, and the person dies. The underlying cause of death in such a case still may be cardiovascular, with a respiratory contributing cause. Schwartz (1994) compared the proportion of deaths by ischemic heart disease with a mention of a respiratory

contributing cause on high- and low-TSP days in Philadelphia and found that mortality with contributing respiratory causes was higher on the high-TSP days. DeLeon and associates (1999) also reported that circulatory and cancer deaths had higher proportions of respiratory contributing causes on higher-PM_{10} days. Thus, some of the observed associations between PM and nonrespiratory underlying causes of death reported in the past and in this study may have been due to contributing respiratory effects.

CONCLUSIONS

Our results generally are not consistent with our study hypothesis that the relative particle-effect size and strength of associations with mortality and morbidity outcomes is, in descending order of magnitude, H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10}, and TSP. The estimated relative risks per equivalent distributional increment often were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for mortality and hospital admission categories. Generally, the PM mass indices (and larger estimated effect size) were associated more significantly with health outcomes (and had larger estimated effect sizes) than H^+ or SO_4^{2-}. When the associations of both H^+ and SO_4^{2-} were significant, SO_4^{2-} was associated more strongly with the outcomes. These results suggest that PM components without H^+ as a constituent are harmful.

Three caveats prevent a simple interpretation of these results: H^+ levels in this data set were low, mostly below the detection limit; the fraction of fine particles in the PM_{10} and TSP was high; and the sample size, especially for the 1992 to 1994 analysis, was relatively small.

Gravimetric PM indices were associated with both respiratory and cardiac hospital admissions and with mortality. Some of these associations may be confounded by O_3, CO, and H^+.

To relate significant associations between health effects and air pollutants to causality requires knowledge of the corresponding errors in relative environmental measurements characterization. Our site-to-site temporal correlation results indicate that the ambient monitors for PM indices and O_3 provide better population exposure estimates than either SO_2 or CO. This may in part explain the stronger associations of PM and $O_3$with health outcomes than demonstrated by other pollutants. That is, these results suggest that spatially homogeneous indicators exhibit stronger associations with health outcomes. However, a more complete assessment of the effects of error in environmental measurements characterization requires knowledge of the relative person-to-monitor error among pollutants, and the current lack of knowledge of such errors precludes this.

Despite the greater measurement error associated with $PM_{10-2.5}$ than with either $PM_{2.5}$ or PM_{10}, this indicator of the coarse particles within the thoracic fraction was associated with some of the outcome measures. This coarse-particle fraction of ambient-air PM is deposited mainly in the conductive airways of the respiratory tract, possibly eliciting responses that appear related to excess hospital admissions and mortality. Future studies will be needed to examine the role of $PM_{10-2.5}$ on specific ICD-9 codes for mortality and morbidity.

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APPENDIX A. Further Characterization of Elderly Respiratory and Circulatory Hospital Admissions (Medicare Data)

In order to characterize the hospital admissions of elderly patients in more detail, we chose the Detroit–Ann Arbor–Flint (Michigan) CMSA. The population for this area in 1990 was 5,187,171. The population for the Detroit MSA was 4,266,654 (Ann Arbor MSA: 490,058; Flint MSA: 430,459).

Those areas constitute the following: (1) Ann Arbor PMSA: Lenawee, Livingston, and Washtenaw counties; (2) Detroit MSA: Lapeer, Macomb, Monroe, Oakland, St Clair, and Wayne counties; and (3) Flint PMSA: Genesee County.

Basic characteristics of the data were examined for the CMSA using 1992 data. We considered this step important for interpretation of the health effects analyses, and also for constructing subcategories. The total admissions during 1992 in the CMSA were 235,371, of which 33.2% were in circulatory categories (ICD-9 390–459), and 10.2% were in respiratory categories (ICD-9 460–519); these were followed by admissions for diseases of the digestive system (ICD-9 520–529) at 9.3% and injury and poisoning (ICD-9 > 800) at 7.9%. We also examined secondary and tertiary causes of admissions. When the primary diagnosis was a circulatory category, in 54% of cases the secondary cause was also circulatory; in 12.3% of cases it was respiratory. However, when the primary cause was respiratory, circulatory and respiratory categories were represented approximately equally as the secondary cause (29% and 31%, respectively). The results were similar for tertiary diagnoses. Although up to ten diagnoses could be recorded, the most frequent number of diagnosis codes recorded was five (44%). The number of diagnosis codes being one, two, three, or four occurred approximately 10% of the time for each.

More females (56%) than males (44%) were admitted. In the CMSA, 78% of admissions were whites; 19%, blacks. Ninety percent of admissions resulted in the discharge of a live patient; 6.6% of the admissions resulted in discharge of a dead patient; and the rest were "still a patient" when discharged. For health effects analysis, we included the discharge records from short-stay hospitals only. Among the types of admission, "emergency" was most frequent (57.8%), followed by "urgent" (17.4%) and "elective" (16.4%). We included only the emergency and urgent admissions for health effects analyses.

Daily counts for the eight respiratory and circulatory categories were then aggregated. Table A.1 shows distributions of daily counts for the eight categories. Among the respiratory categories, pneumonia had the largest daily counts, and its distribution was also most skewed due to the influenza epidemics. There were generally more admissions for circulatory categories. Ischemic heart disease had the largest mean daily counts (53/day), followed by heart failure (mean = 37/day).

We also examined age distribution of admissions in these categories (Figure A.1). Note that the small fraction (< 7%) of admissions of patients younger than 65 was eliminated. The mode was at approximately the mid- to late 70s for patients with pneumonia, dysrhythmias, and heart failure, whereas the mode was at about age 70 for patients with COPD and ischemic heart disease. If the age category needs to be divided further, a cutoff at 75 years old would split the counts into approximately equal numbers of daily admissions.

Table A.1. Distribution of Respiratory and Circulatory Admissions Between 1992 and 1994

Category	25%	50%	75%	Mean	Max
Pneumonia	19	24	29	25	106
COPD	13	17	21	17	54
Ischemic heart disease	45	54	62	53	95
Dysrhythmias	12	16	19	16	33
Heart failure	30	36	43	37	72
Stroke	25	29	34	29	52

EXAMINATION OF MULTIPLE ADMISSIONS

Unlike daily mortality counts, emergency hospital admissions data can have multiple contributions from a single patient. Although this phenomenon does not negate the adverse effects of pollution, its extent may alter the interpretation of the estimated relative risks. The extent of multiple admissions has not been well documented in

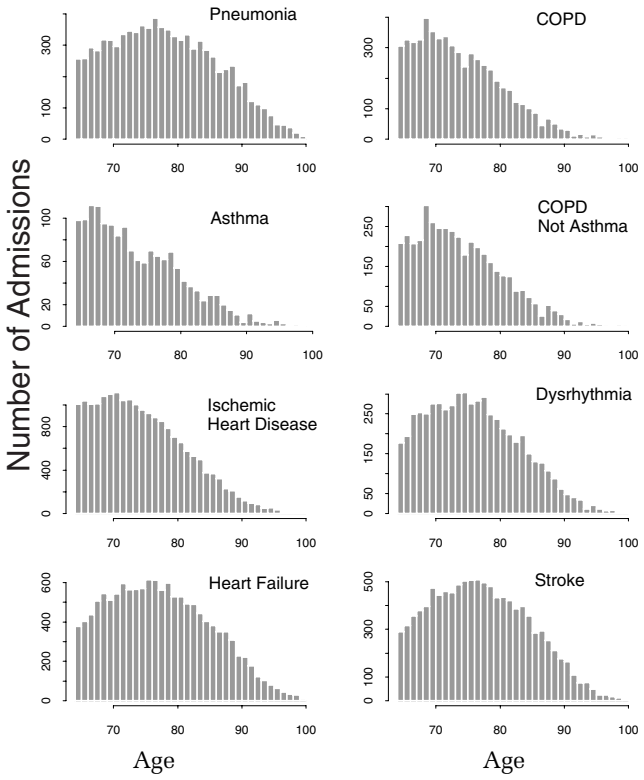


Figure A.1. Age distribution of respiratory and circulatory admissions.

Table A.2. Number of Hospital Admissions by Individuals 1992–1994[a]

Category	25%	50%	75%	95%	Mean	Max	Total Persons	Total Counts
Pneumonia	1	1	1	2	1.17	14	24,673	28,887
COPD	1	1	2	4	1.58	29	12,659	20,020
Ischemic heart disease	1	1	2	3	1.44	41	41,846	60,339
Heart failure	1	1	2	4	1.55	20	26,773	41,533
Dysrhythmias	1	1	1	2	1.18	8	15,304	18,088
Stroke	1	1	1	2	1.15	7	28,758	33,256

[a] Large extreme numbers are of interest.

time-series studies to date. Because the health insurance claim number in the HCFA records uniquely identifies a Medicare beneficiary, multiple admissions of a single person could be computed.

For each of the eight respiratory and cardiovascular subcategories, we computed the number of admissions per person (Table A.2) and the interval between the multiple admissions (Table A.3) for the study period 1992 to 1994. In examining the distribution of multiple admissions, our interest is that fraction of elderly patients who had many admissions, as this may influence the overall estimated relative risk. We are also interested in the temporal clustering of multiple admissions, as this may cause autocorrelation. In every category, at least 50% of the individuals had only one admission over the three years. Among the respiratory categories, pneumonia had the fewest multiple admissions, with only 5% of individuals having been admitted more than twice during the study period. Over a quarter of the individuals with COPD were admitted more than twice during the three years. Among the circulatory categories, more than a quarter of patients in both ischemic heart disease and heart failure categories had been admitted more than twice during the study period.

Table A.3. Number of Days Separated for Each Consecutive Pair of Multiple Hospital Admissions by Individuals[a]

	Percentile					
Category	5	10	25	50	75	Mean
Pneumonia	14	21	46	125	306	206
COPD	13	20	41	101	234	168
Ischemic heart disease[a]	2	3	8	59	215	150
Heart failure	12	17	34	84	210	156
Dysrhythmias	3	7	22	94	287	187
Stroke	5	12	39	132	323	213

[a] Lower percentiles are of interest because of possible contribution to autocorrelation.

The distribution of the interval between the multiple admissions (Table A.3) varied among the categories. Circulatory categories, except heart failure, tended to show shorter intervals than respiratory categories. The ischemic heart disease category had the shortest interval, with a quarter of the readmissions (roughly one-eighth of the total admissions in this category) occurring within eight days. Intervals between admissions for the respiratory categories were longer, with less than 10% of the multiple admissions occurring within a three-week period. Currently we do not know the implication of these multiple admissions for the estimated air pollution risks. Because the extent is not negligible, and the readmissions do occur within a short period (< 7 days) of time for some people, it seems important to investigate this issue further. We can, for example, include only those who had a single admission during the three years, or we can restrict each individual's admissions to only the first one during the study period.

LENGTH OF STAY AND ADMISSIONS RESULTING IN DEATH

We also are interested in the length of hospital stay and the fraction of admissions that resulted in death, because both reflect the severity associated with the admissions. Also, they may provide insight into the lag structure linking admissions and deaths. We examined these variables using 1992 data for the CMSA. The discharge status coded in the records had three categories: discharged alive, discharged dead, and still a patient. We examined these data also to see if we had enough sample size to carry out health effects analyses linking admissions and deaths (this is separate from the mortality analysis for 1992 to 1994 using NCHS data).

Table A.4 shows the percentages of admissions that resulted in death for each of the eight admission categories. The highest mortality rate was for pneumonia admissions (14.2%), followed by stroke (9.1%) and heart failure (8.3%). It should be noted that these numbers are not adjusted for multiple admissions; therefore, mortality rate per individual would be higher. The mortality rates correspond to

Table A.4. Median Length of Stay (MLS) and Mortality Rate for Respiratory and Circulatory Categories, 1992

Category	Discharged Dead (%)	MLS for All Discharges	MLS for Discharged Dead
Pneumonia	14.2	9	7
COPD	5.3	6	9
Ischemic heart disease[a]	6.2	5	4
Dysrhythmias	5.6	4	2
Heart failure	8.3	6	7
Stroke	9.1	7	6

3 to 4 daily deaths for pneumonia, ischemic heart disease, heart failure, and stroke, and about 1 death per day for COPD and dysrhythmias. These death counts may be too small for a time-series analysis with three years of data and small relative risks (ie, 1.03 per 50 $\mu g/m^3$ increase in PM_{10}) reported for total deaths in the past. However, separate analyses of these mortality data may be worthwhile because relative risks may be larger for elderly patients with specific compromised conditions. Other analyses (eg, logistic regressions) might provide links to exposure while controlling for fixed and time-varying covariates. We are examining these possibilities.

Table A.4 also shows the median length of stay for all discharges and for the admissions that resulted in death. The longest median length of stay for all discharges (alive and dead) was for pneumonia (9 days), and the shortest median length of stay was for dysrhythmias (4 days). The length of stay for admissions resulting in death (discharged dead) could be either longer or shorter than the length of stay for the other two categories of discharge, depending on the category of admission. The shortest median length of stay for the discharged dead was for dysrhythmias (2 days), followed by ischemic heart disease (4 days). Median length of stay for the rest of the categories was longer than 6 days. That is, at least for a major fraction of the admissions resulting in deaths, the lagged periods from admission to death were longer than the lags reported in most mortality studies (0 to 5 days). Thus, the majority of people who died after being admitted to hospitals are unlikely to be those whose deaths are associated with elevated levels of air pollution with 0- to 5-day lags.

APPENDIX B. 1992–1994, Detroit–Ann Arbor–Flint CMSA: PM_{10}. Effects of Multiple Hospital Admissions on Estimated PM_{10} Relative Risks

BACKGROUND

Unlike the case for daily mortality, a person can contribute multiple counts to daily emergency hospital admissions (see Appendix A). Although this phenomenon does not negate the adverse effects of air pollution, its extent may alter the interpretation of the estimated relative risks obtained from aggregate time-series analyses.

Medicare records with individual identifiers allowed us to investigate this issue by constructing separate time series for those who had multiple admissions and those who had only a single admission during the three-year study period. The individual records also made it possible to characterize the subpopulations by race, age, and gender.

METHODS

Unscheduled hospital admissions in elderly patients (from Medicare data) for pneumonia (ICD-9 480–486) and COPD (ICD-9 490–496) from the Detroit–Ann Arbor–Flint metropolitan area from 1992 to 1994 were retrieved from the HCFA's MEDPAR file. Data on PM_{10} for the metropolitan area were retrieved from the EPA's AIRS database. Data from multiple sites were averaged for this analysis.

For COPD and pneumonia subcategories, we constructed separate time series for those who had only one hospital admission over the study period and for those who had multiple admissions, on the basis of claim ID numbers. We also characterized these two populations in terms of age, race, and gender.

The effects of air pollution were estimated using GAM Poisson regressions, adjusting for temporal trends (including seasonal cycles), temperature, and day of week. Temporal trends were modeled using smoothing splines of time (day) corresponding to a periodicity of 1 month or longer. Both hot (same-day) and cold (average of 1- to 3-day lags) temperatures were modeled with LOESS smoothing. Various lags and averaging periods also were modeled for pollution variables.

RESULTS

There were no substantial differences in age, race, and gender characteristics between the single and multiple admission groups, except that more males had multiple admissions for pneumonia, and younger and nonwhite groups had more multiple admissions for COPD (Table B.1).

Table B.1. Characteristics of Single Versus Multiple Hospital Admission Subgroups

Category	Median Age (Years)	Sex (%)		Race (%)	
		Male	Female	White	Nonwhite
Pneumonia					
Single admission	78	45	55	81	19
Multiple admission	78	52	48	80	20
COPD					
Single admission	74	42	58	82	18
Multiple admission	72	41	59	77	23

PM_{10} was the index associated most consistently with these admission series, with a 1-day lag most consistently significant. The resulting GAM model fits for COPD are shown in Figure B.1.

As seen in Table A.2, the extent of multiple admissions for pneumonia was not substantial, with average admissions per individual of 1.17. The PM relative risk estimates per interquartile range for populations with multiple admissions (RR = 1.045; 95% CI 1.012–1.080) and single admissions (RR = 1.041; 95% CI 1.021–1.062) were comparable. For COPD, however, the number of multiple admissions was substantial (average admissions per person = 1.58). The PM relative risk estimate for the population with multiple admissions (RR = 1.013; 95% CI 0.986–1.040) was smaller

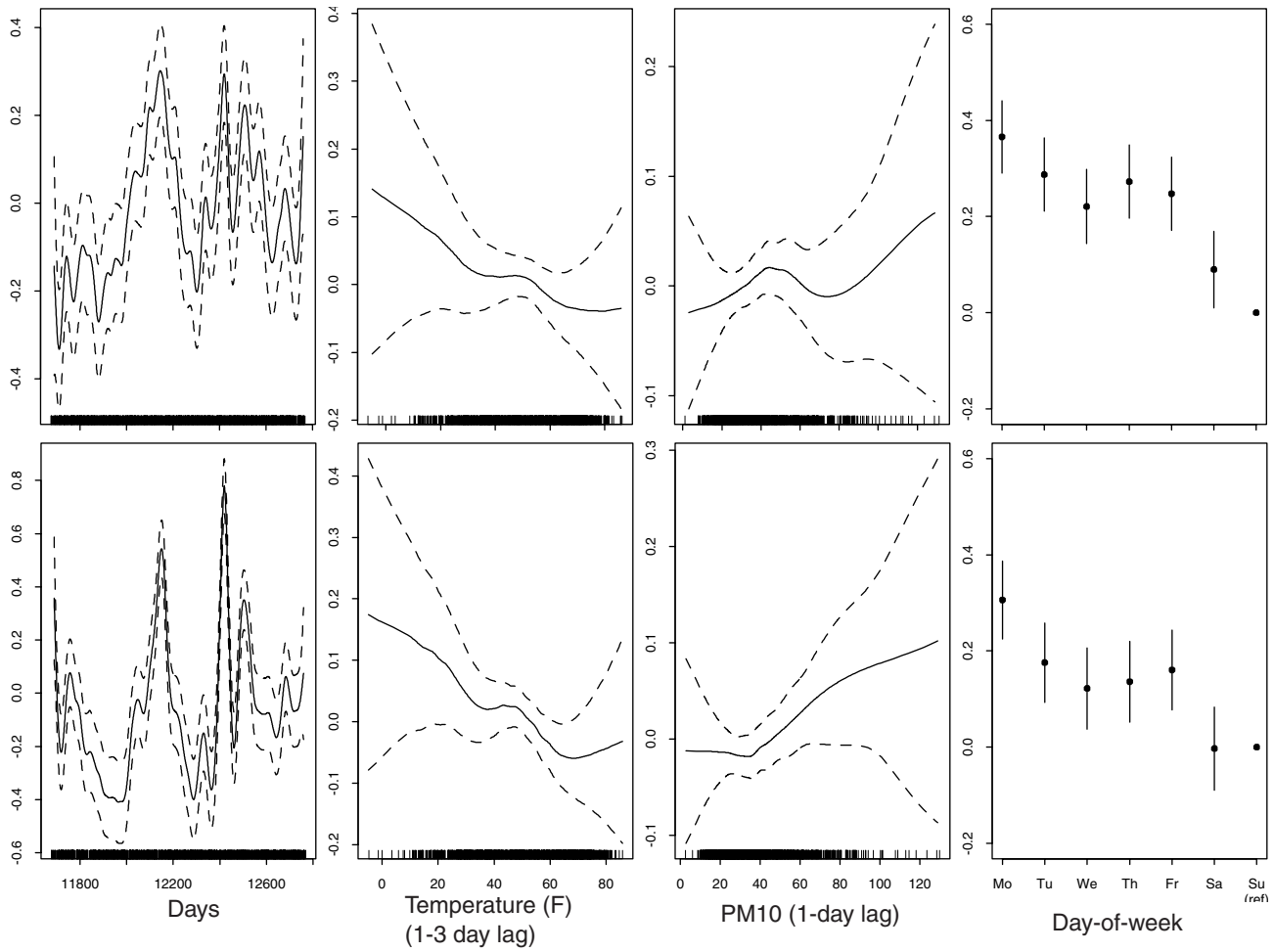


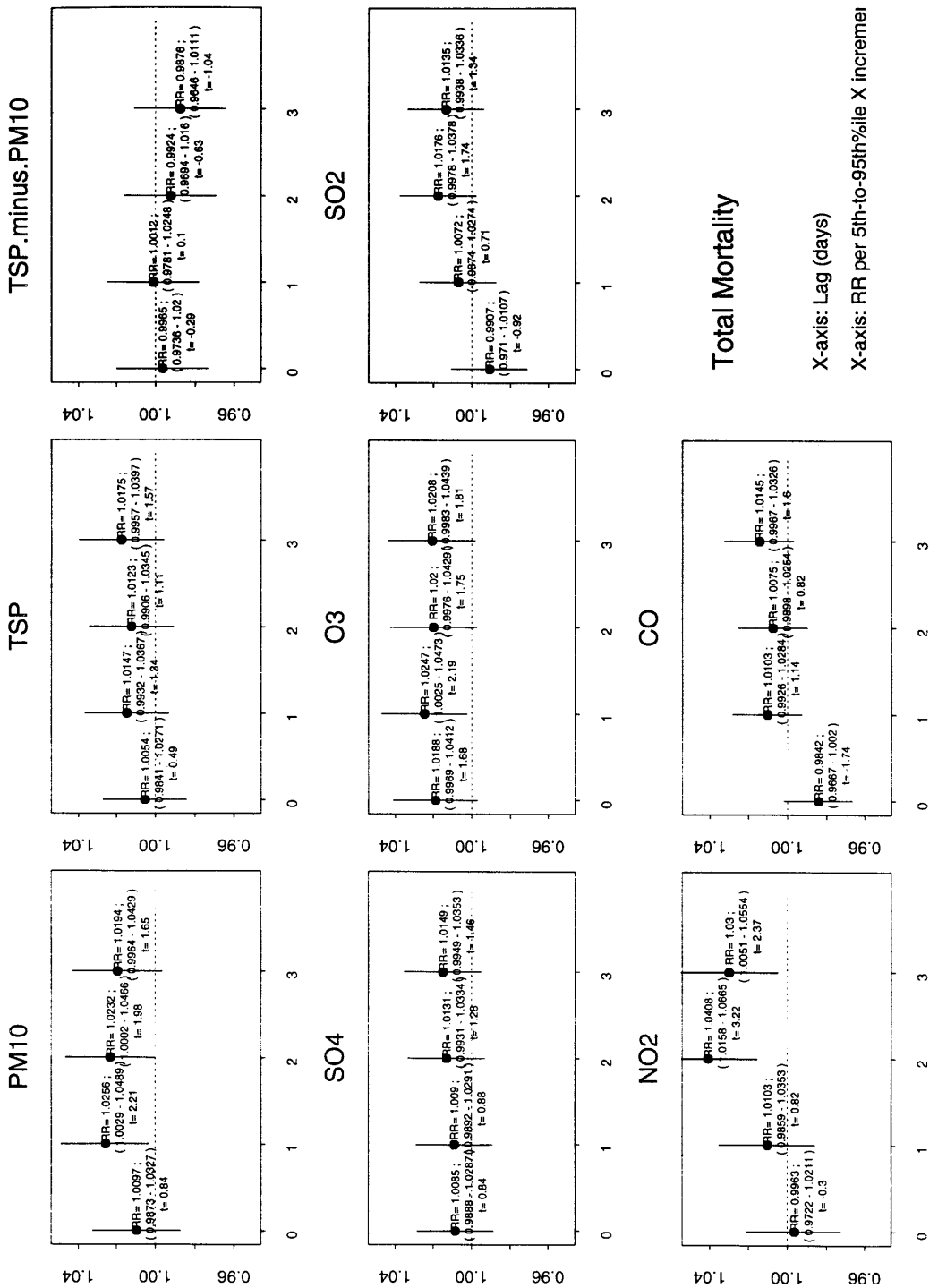
Figure B.1. GAM Poisson regression results for hospital admissions among subjects with COPD. Top panels = multiple admissions per subject; bottom panels = single admission per subject over study period.

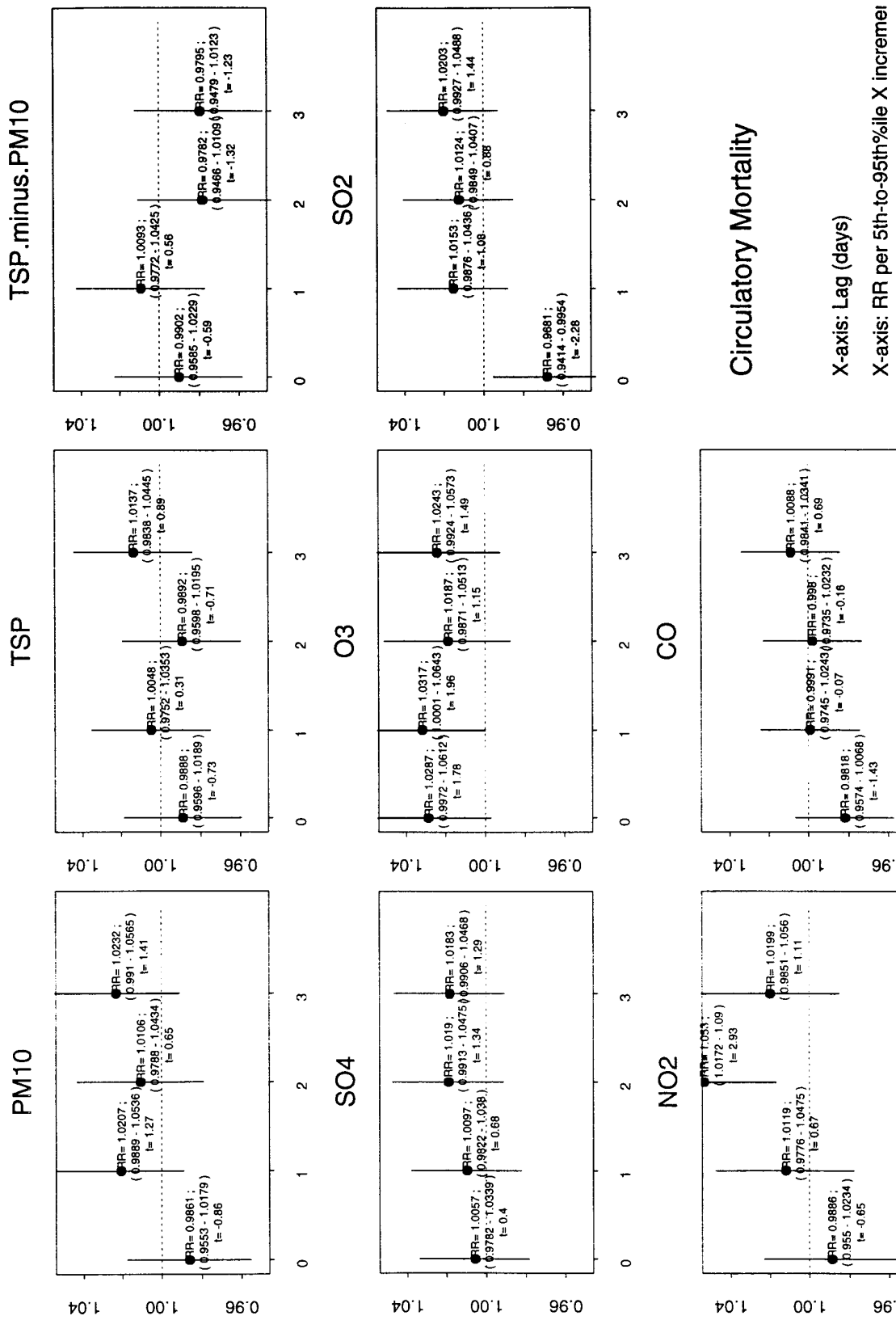
than that for the population with single admissions (RR = 1.039; 95% CI 1.009–1.071).

DISCUSSION

These results suggest that the estimated PM relative risks for the entire elderly population in this metropolitan area are not seriously distorted by the effects of the subgroup with multiple admissions.

APPENDIX C. Relative Risks Estimated for All Lag/Averages for 1985–1990 Analysis




TSP.minus.PM10
SO2
TSP
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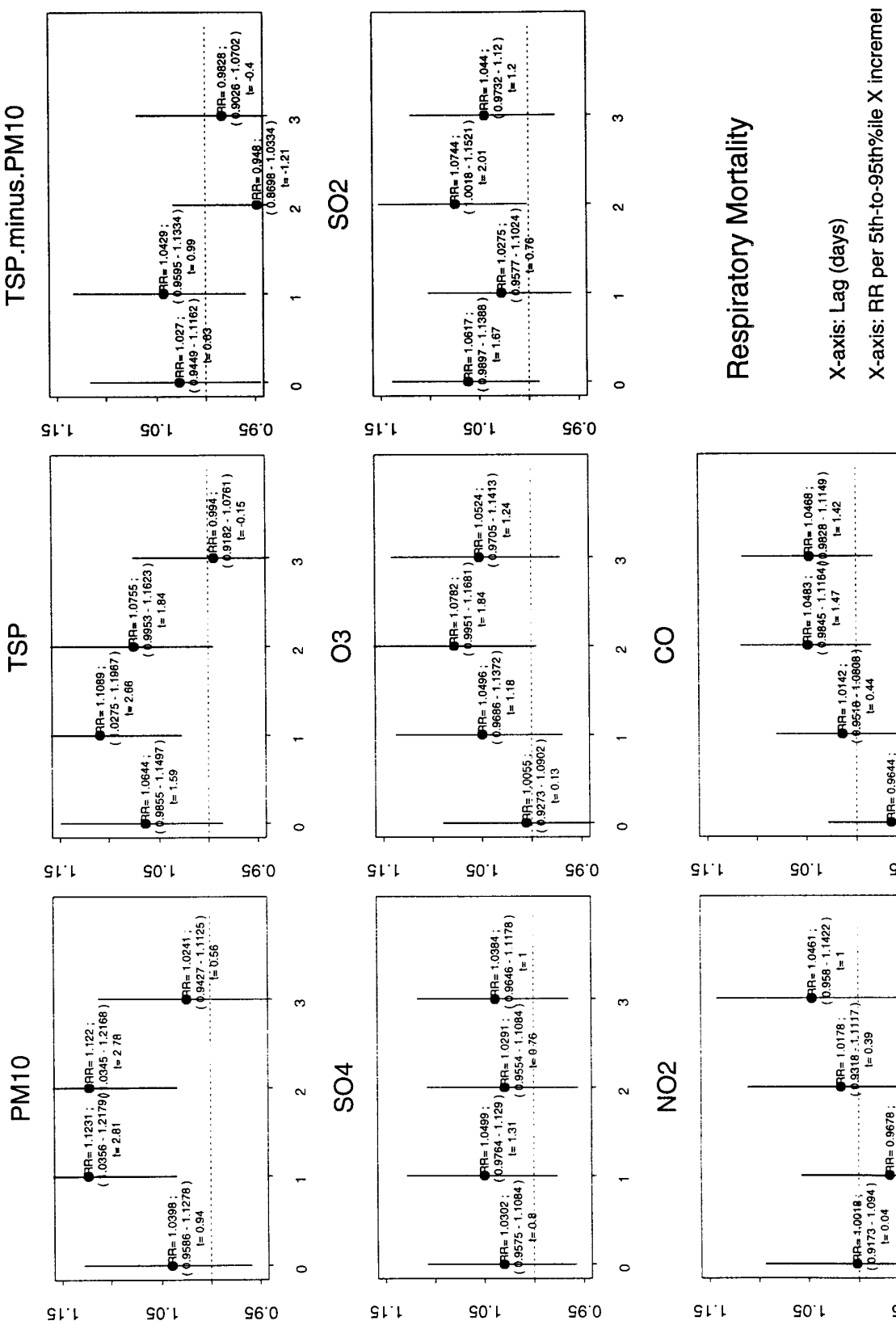
Circulatory Mortality
X-axis: Lag (days)
X-axis: RR per 5th-to-95th%ile X increme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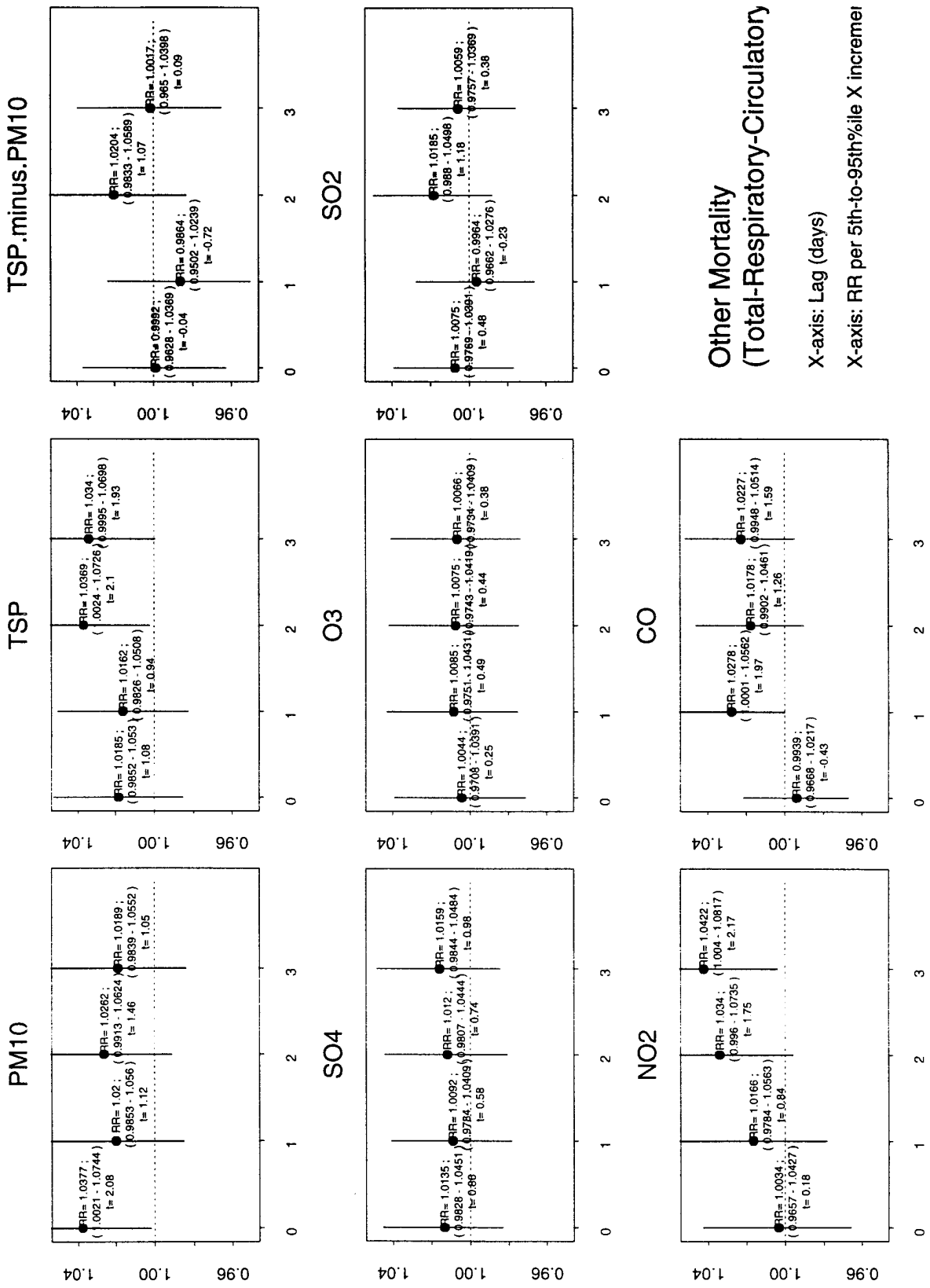
Respiratory Mortality
X-axis: Lag (days)
X-axis: RR per 5th-to-95th%ile X increme


TSP.minus.PM10
TSP
SO2
PM10
O3
CO
SO4
NO2
Other Mortality
(Total-Respiratory-Circulatory
X-axis: Lag (days)
X-axis: RR per 5th-to-95th%ile X increme
0.96
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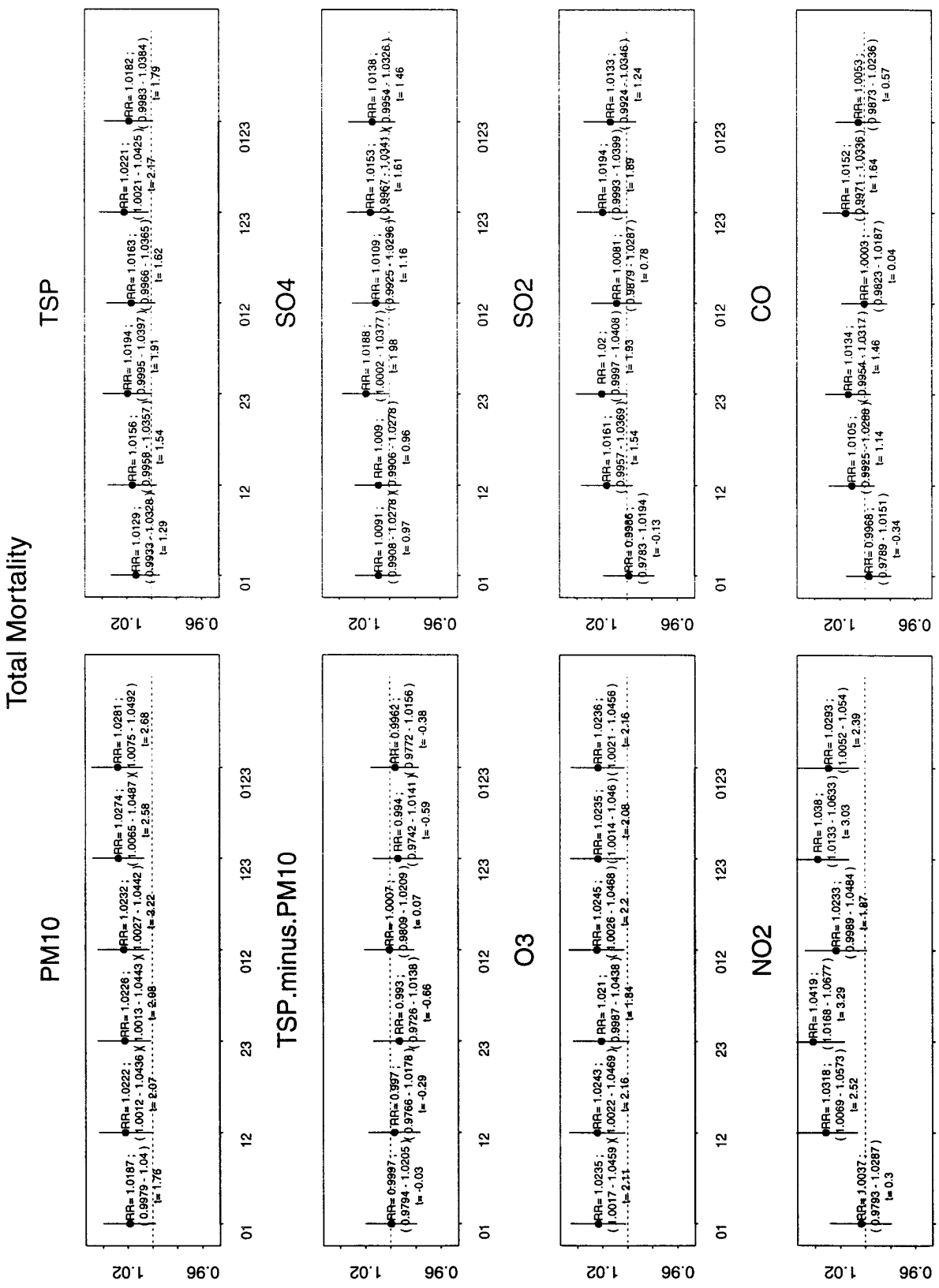
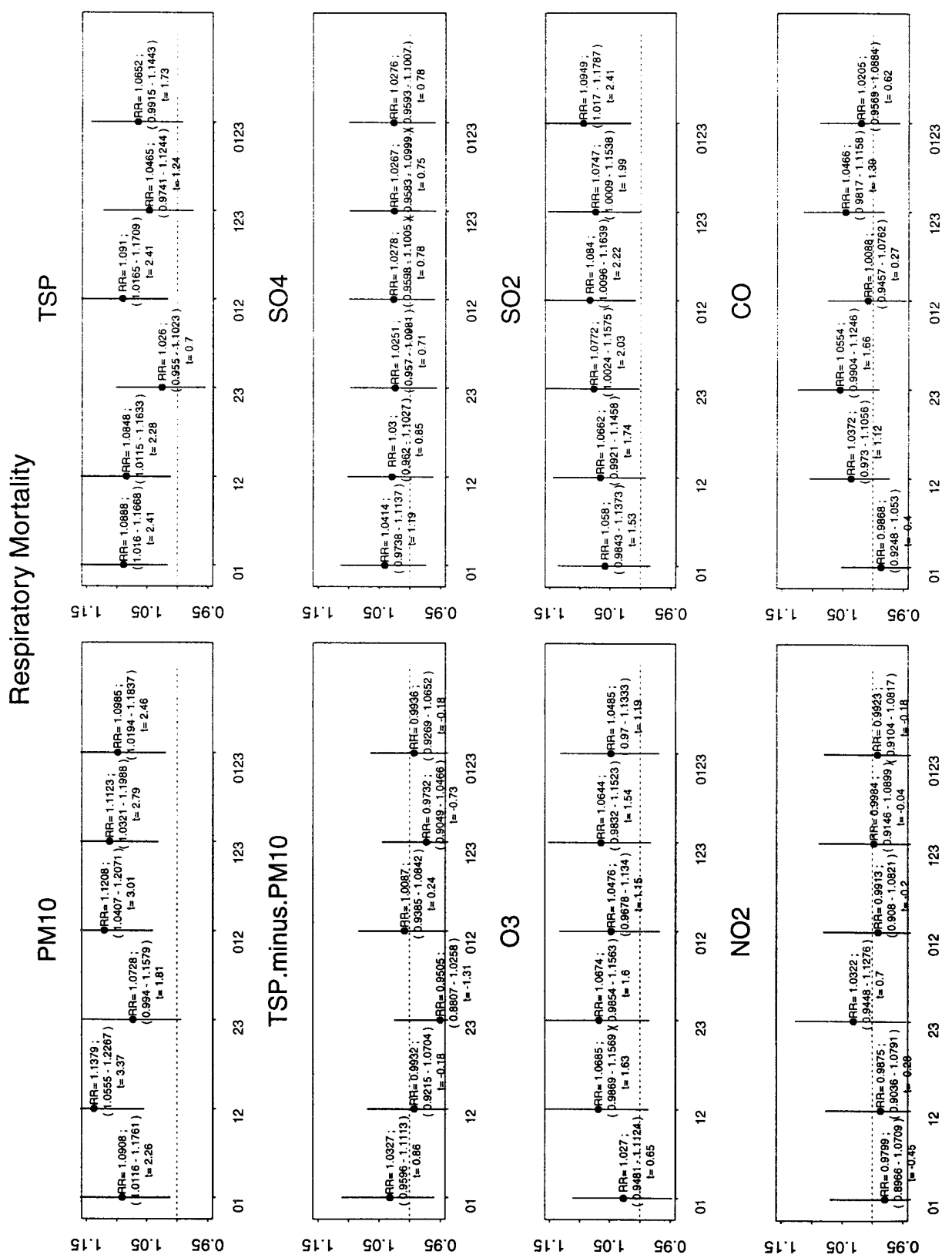
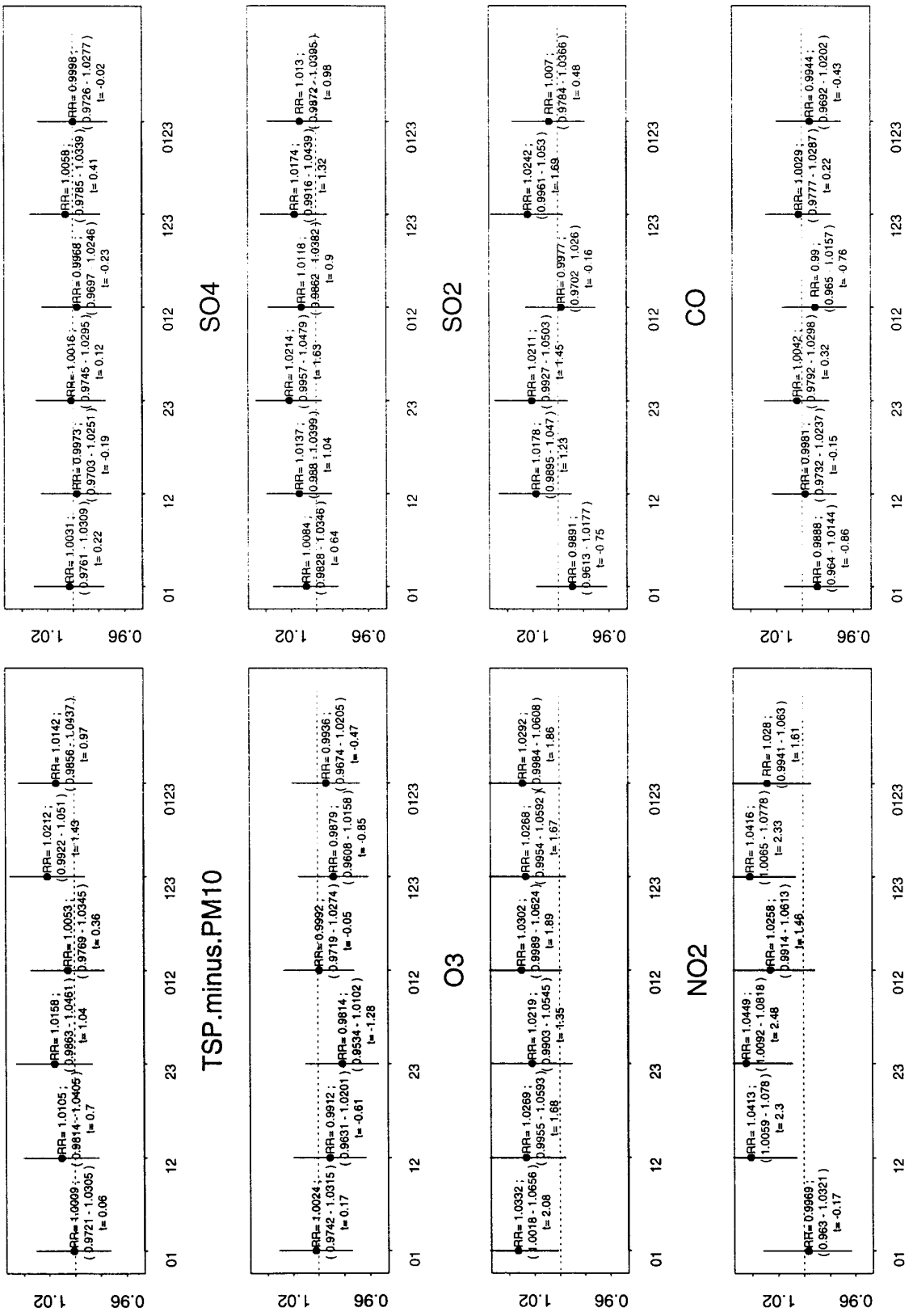
1.04
0
1
2
3


Total Mortality
PM10
TSP
TSP.minus.PM10
SO4
O3
SO2
NO2
CO


Respiratory Mortality
PM10
TSP
TSP.minus.PM10
SO4
O3
SO2
CO
NO2


Circulatory Mortality
PM10
TSP
TSP.minus.PM10
SO4
O3
SO2
NO2
CO
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01
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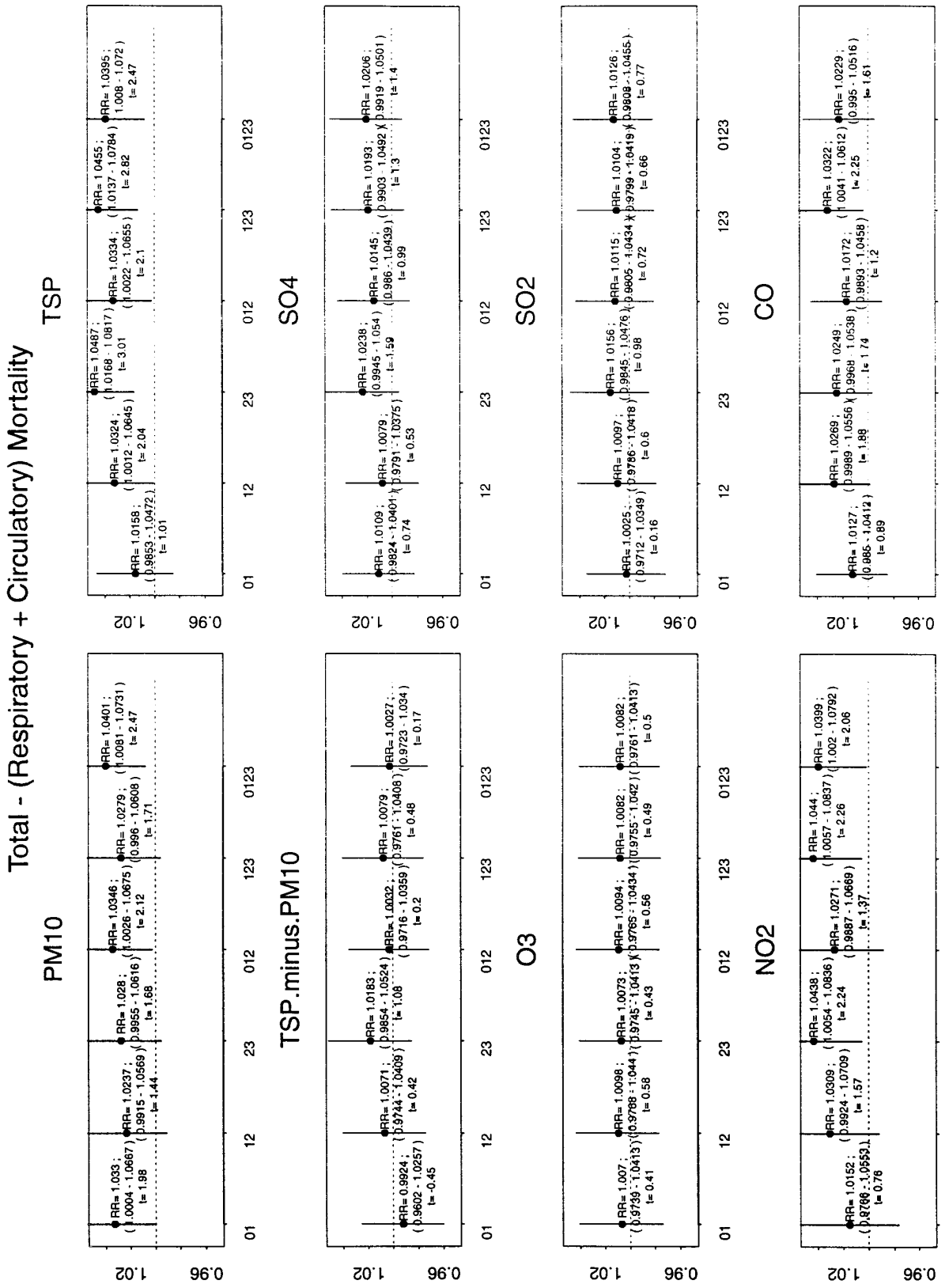
Total - (Respiratory + Circulatory) Mortality
PM10
TSP
TSP.minus.PM10
SO4
O3
SO2
NO2
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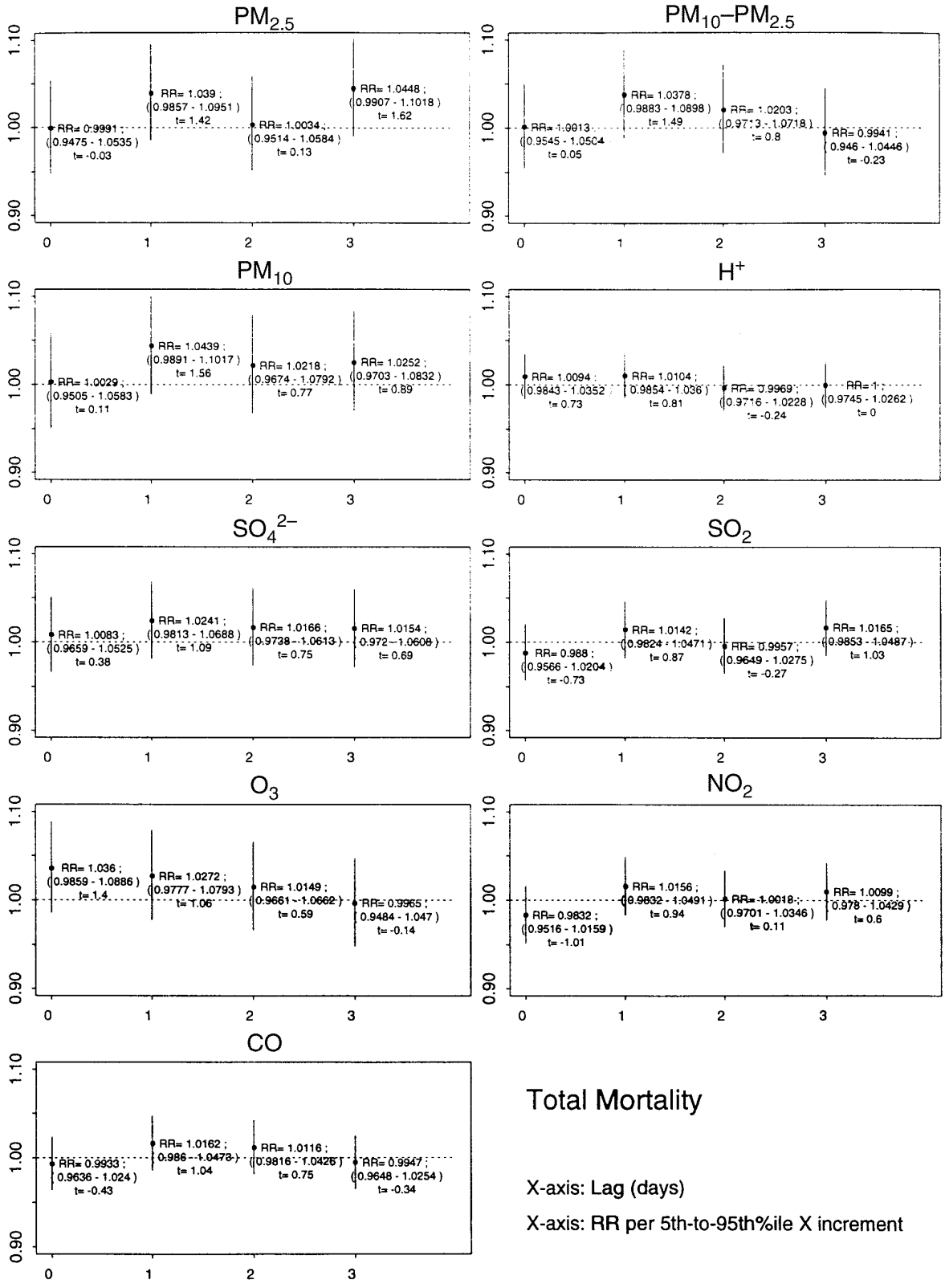
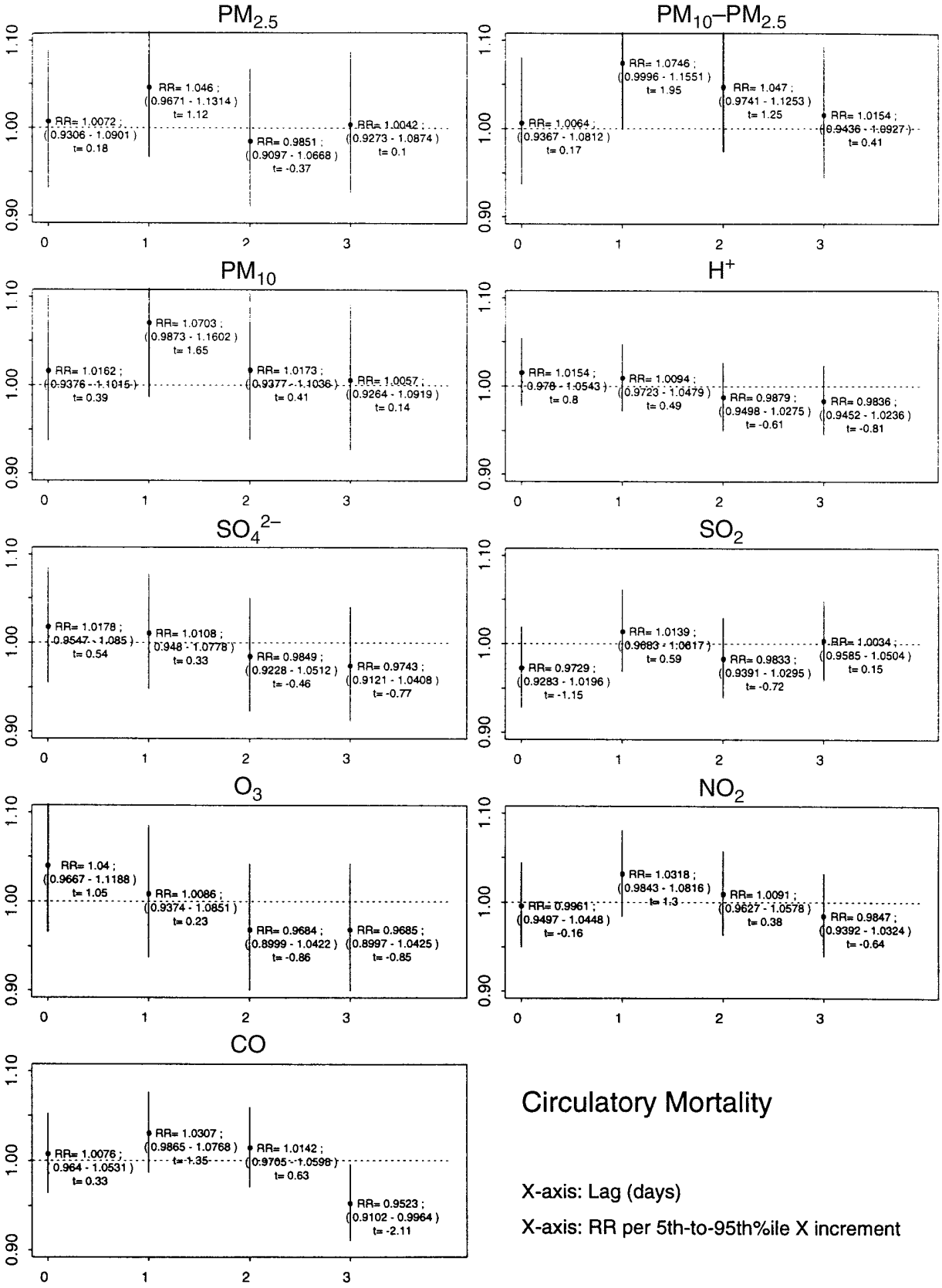
APPENDIX D. Relative Risks Estimated for All Lag/Averages for 1992–1994 Analysis

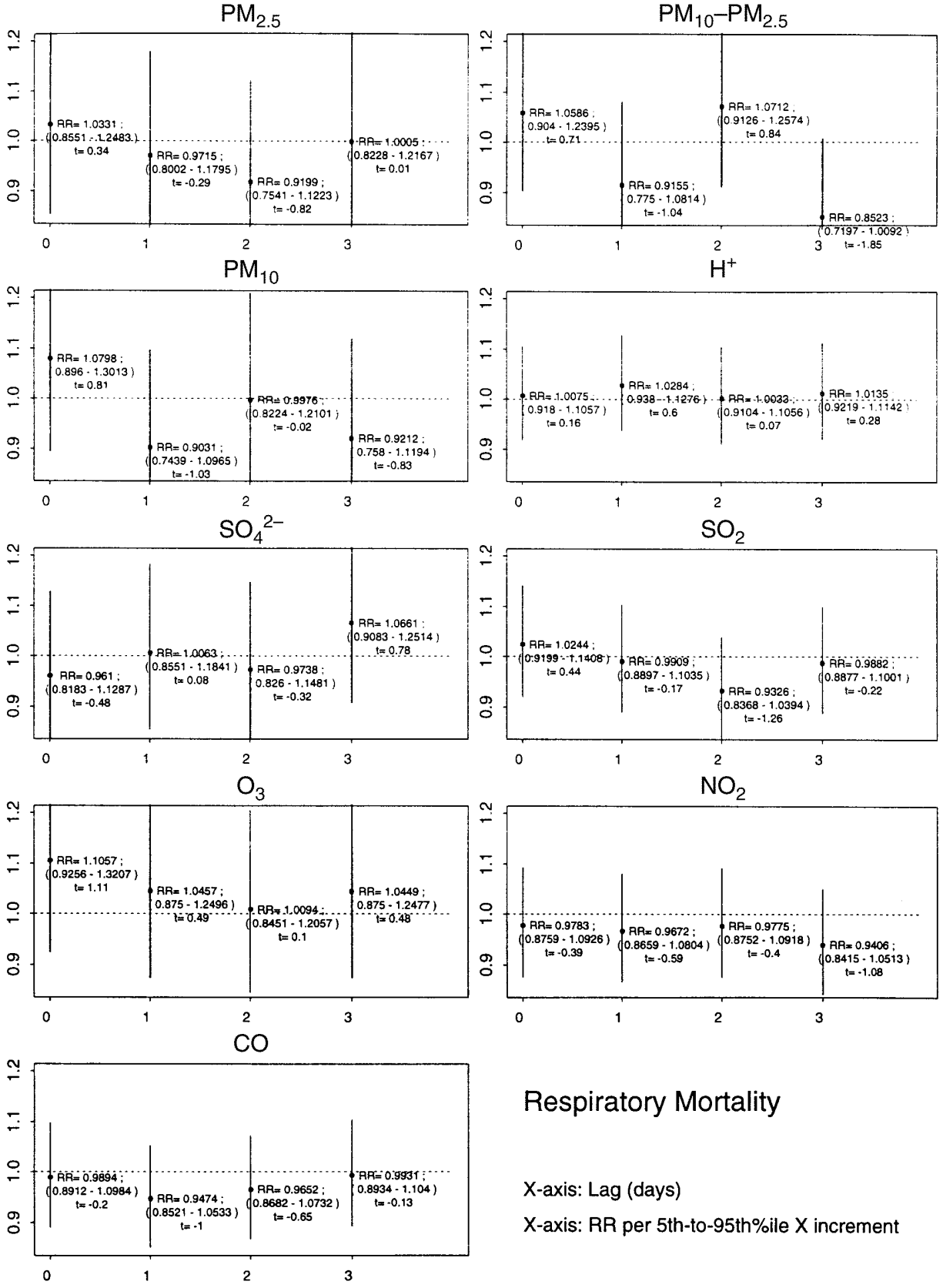




Circulatory Mortality

X-axis: Lag (days)

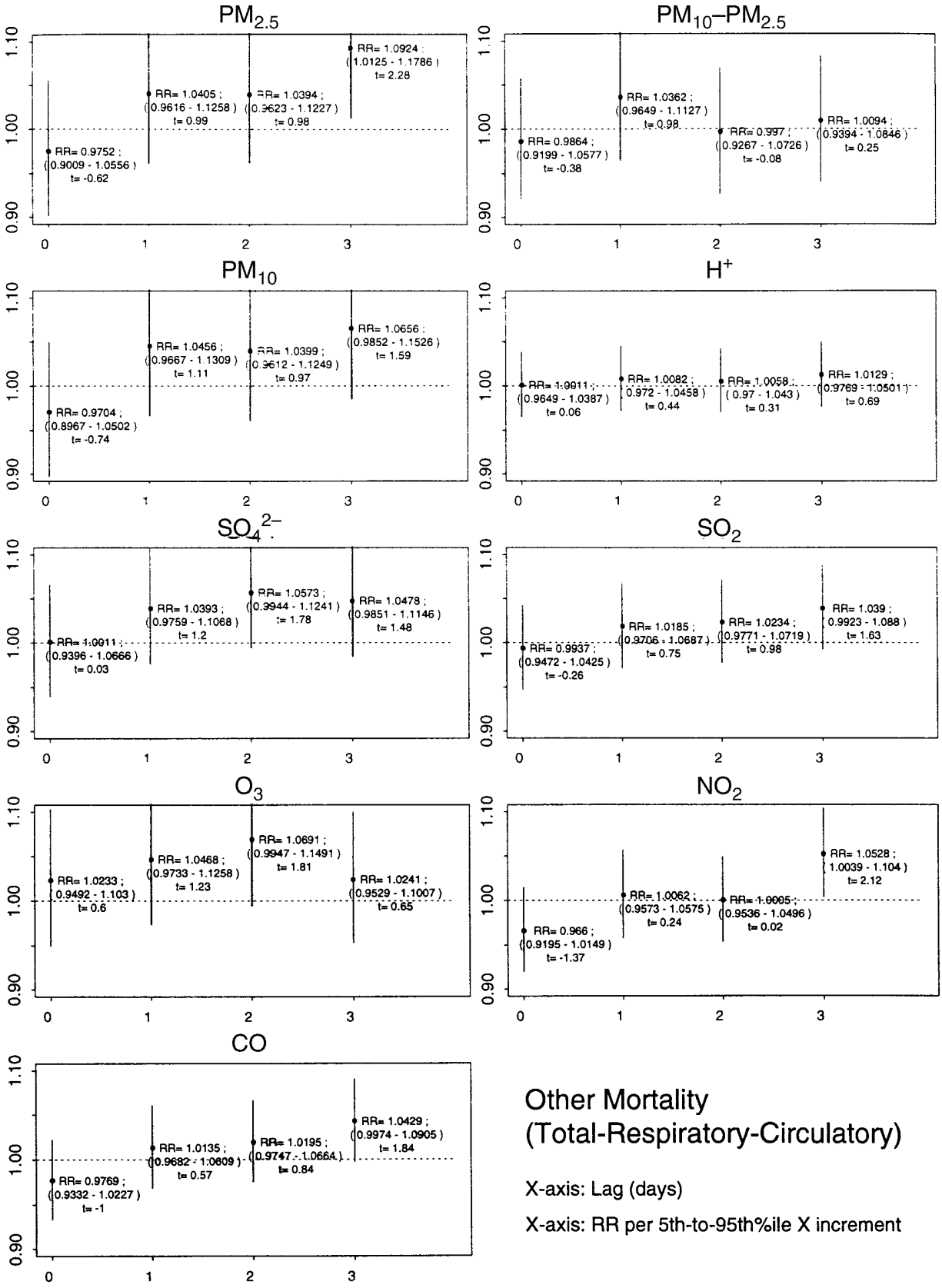
X-axis: RR per 5th-to-95th%ile X increment



Respiratory Mortality

X-axis: Lag (days)

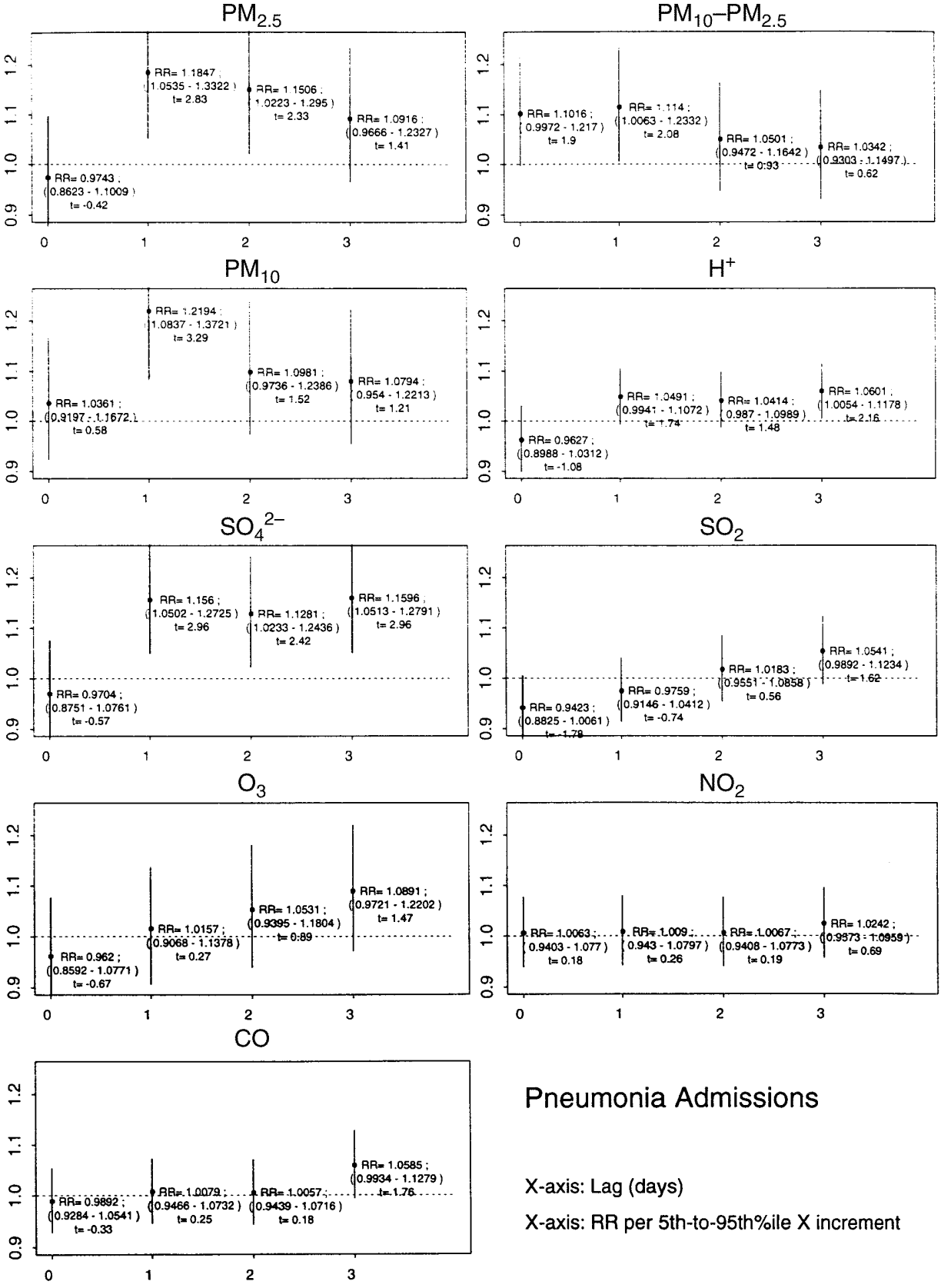
X-axis: RR per 5th-to-95th%ile X increment



Other Mortality
(Total-Respiratory-Circulatory)

X-axis: Lag (days)

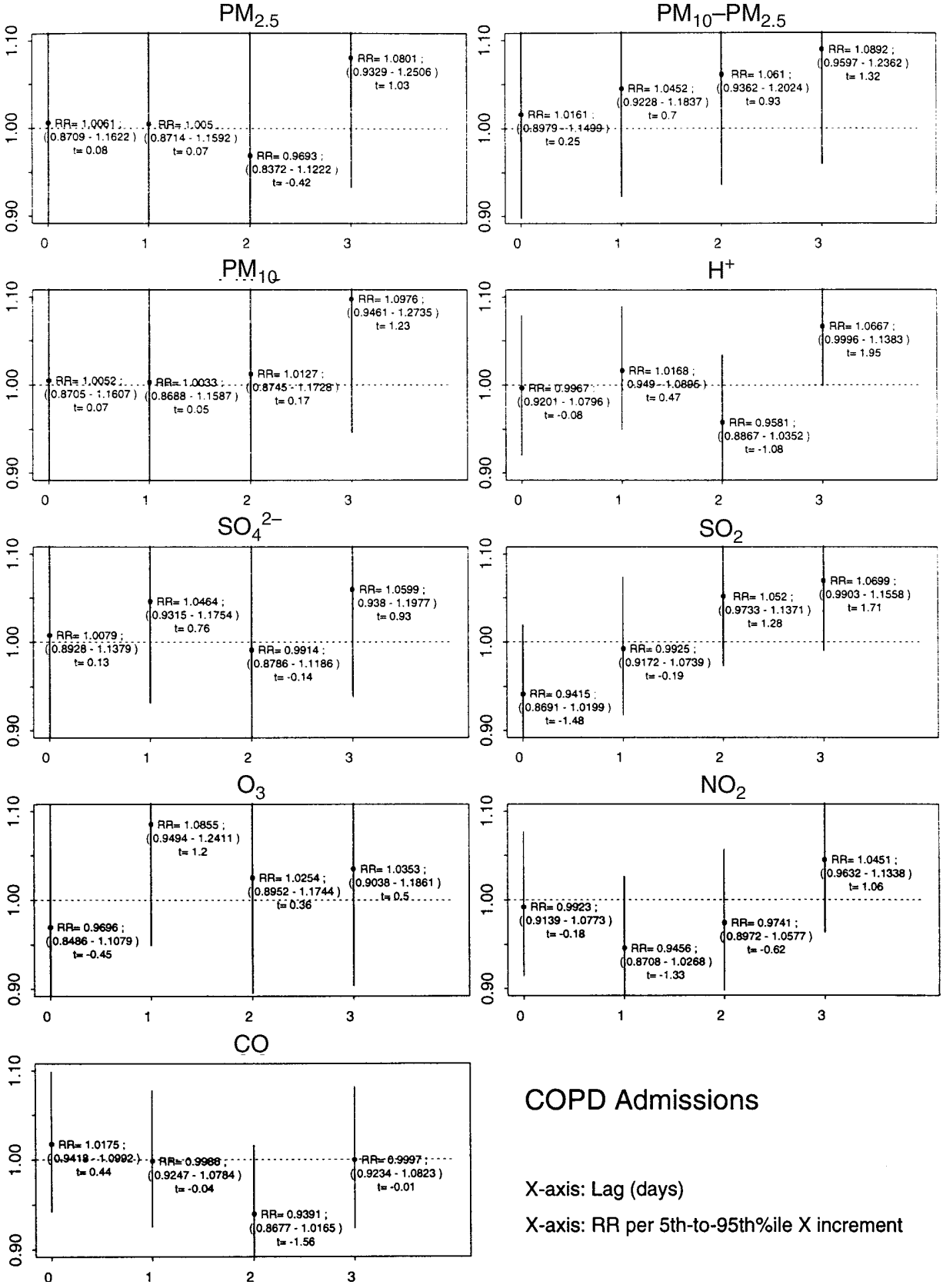
X-axis: RR per 5th-to-95th%ile X increment



Pneumonia Admissions

X-axis: Lag (days)

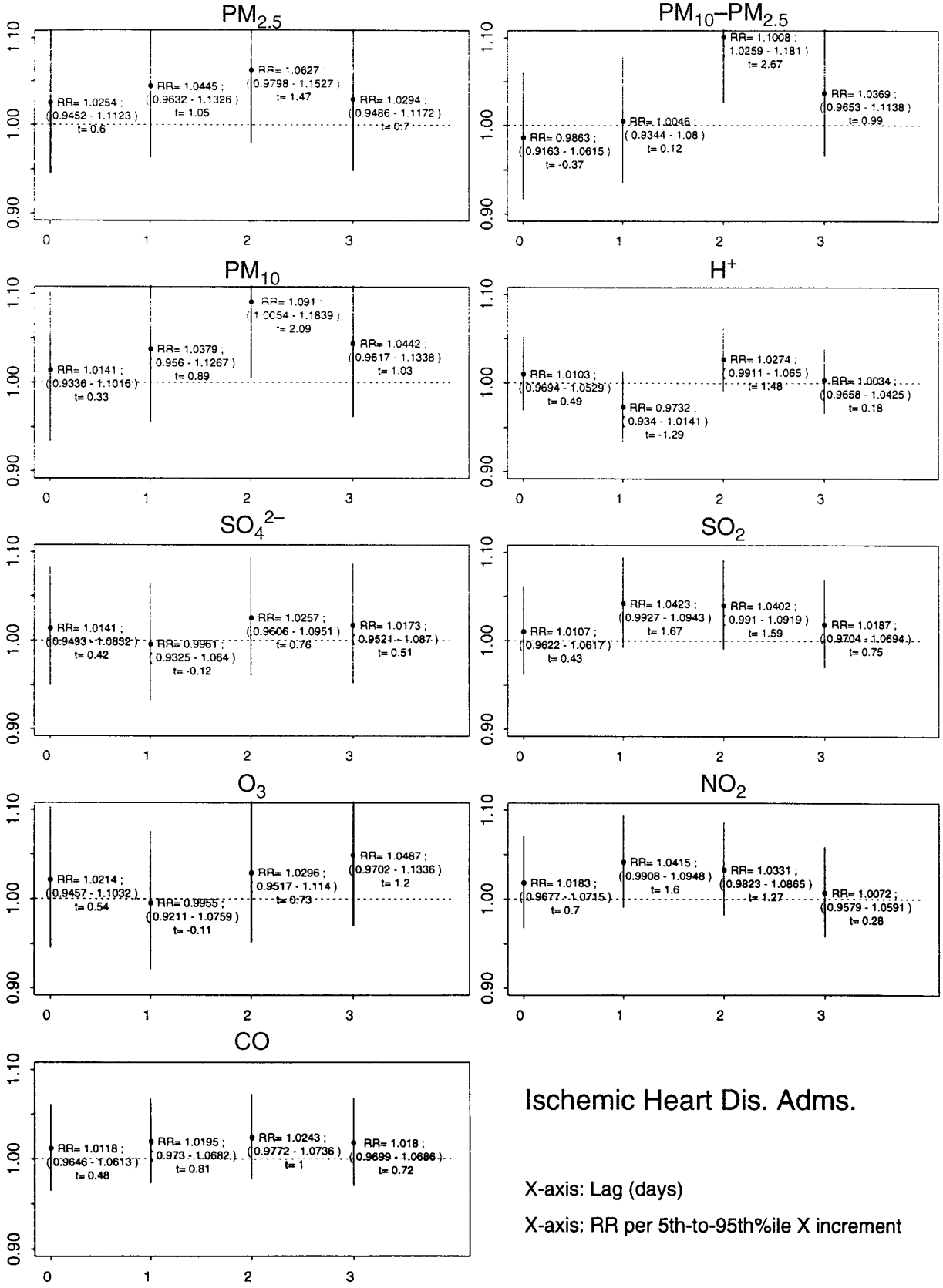
X-axis: RR per 5th-to-95th%ile X increment



COPD Admissions

X-axis: Lag (days)

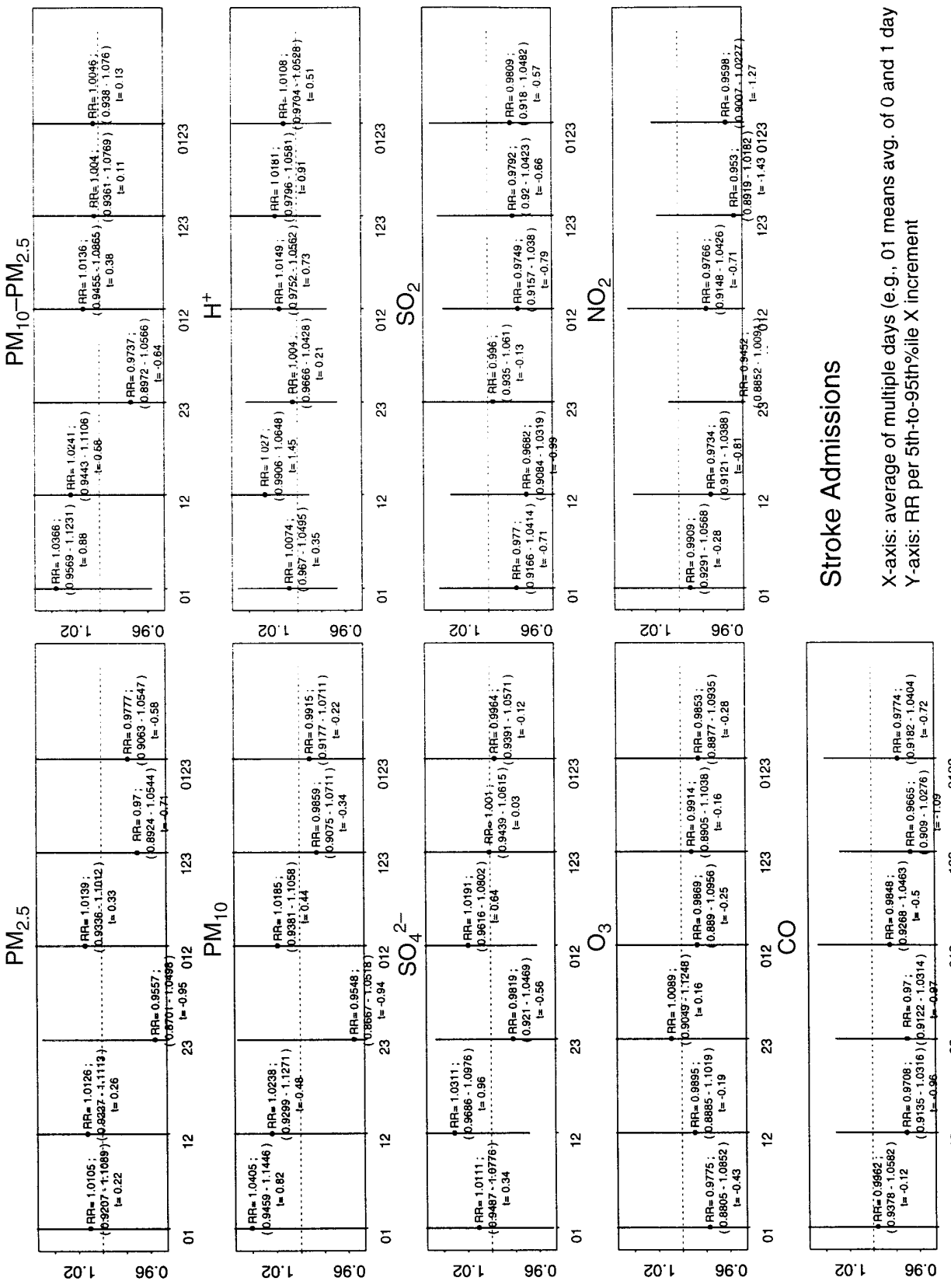
X-axis: RR per 5th-to-95th%ile X increment

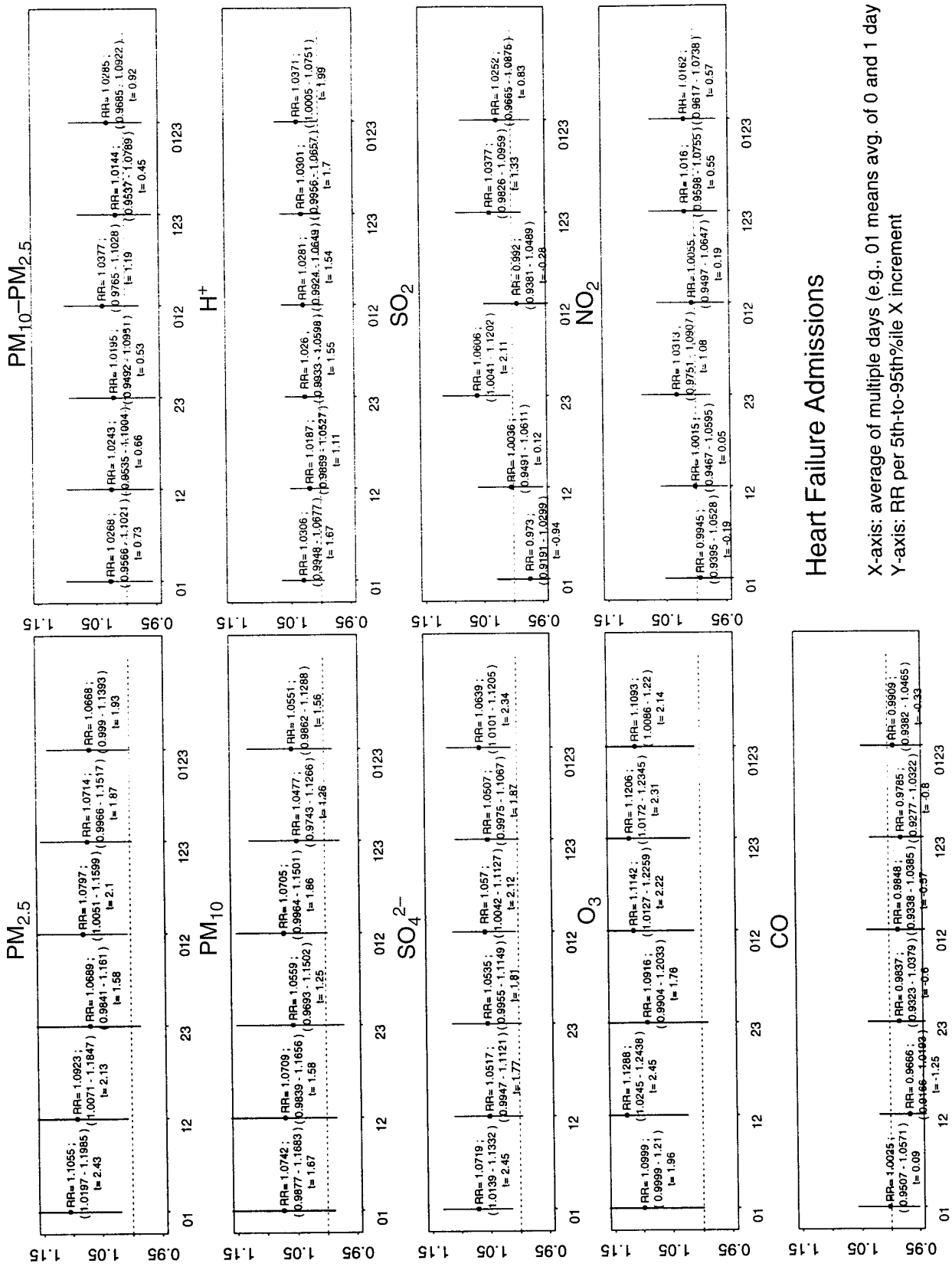


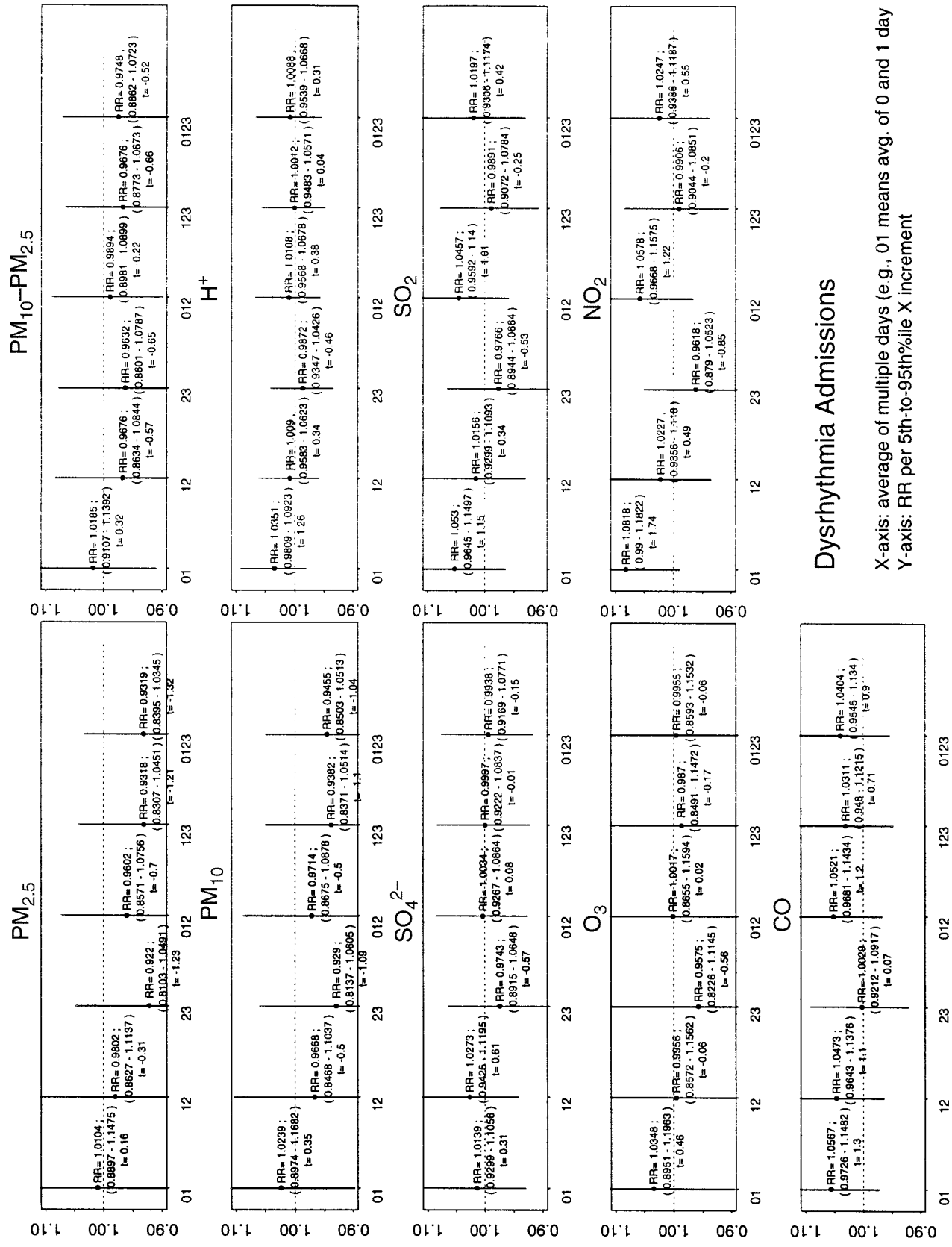
Ischemic Heart Dis. Adms.

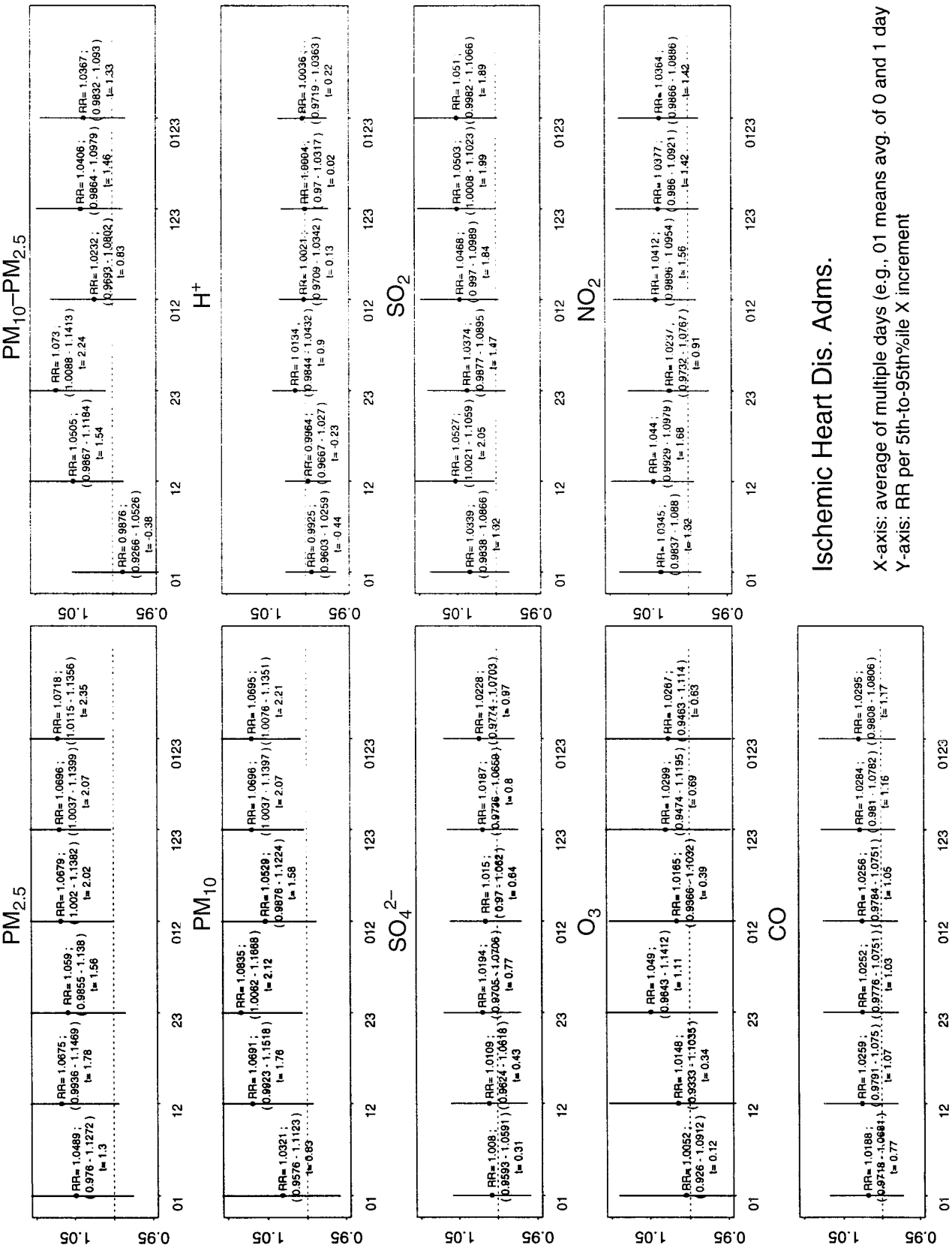
X-axis: Lag (days)

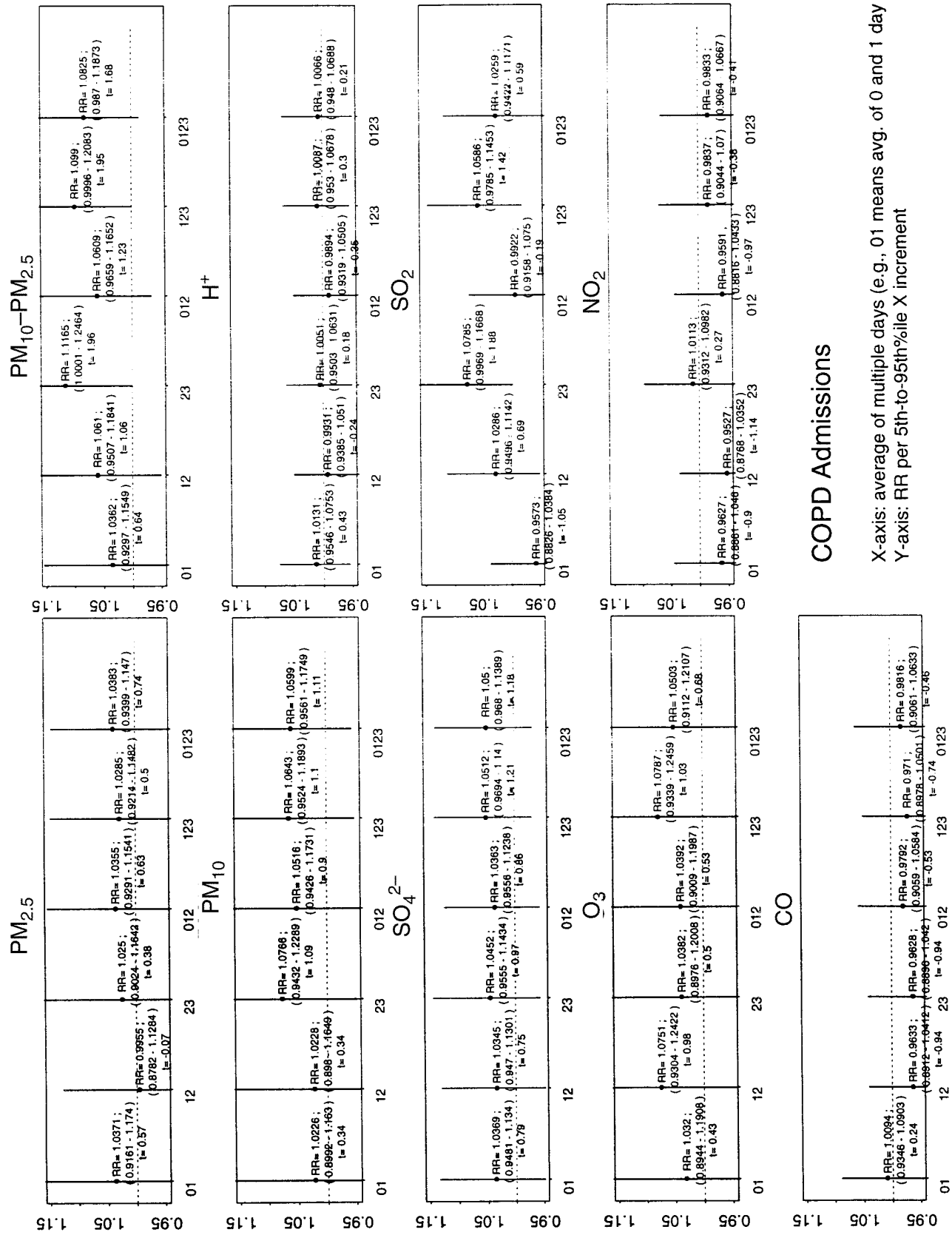
X-axis: RR per 5th-to-95th%ile X increment

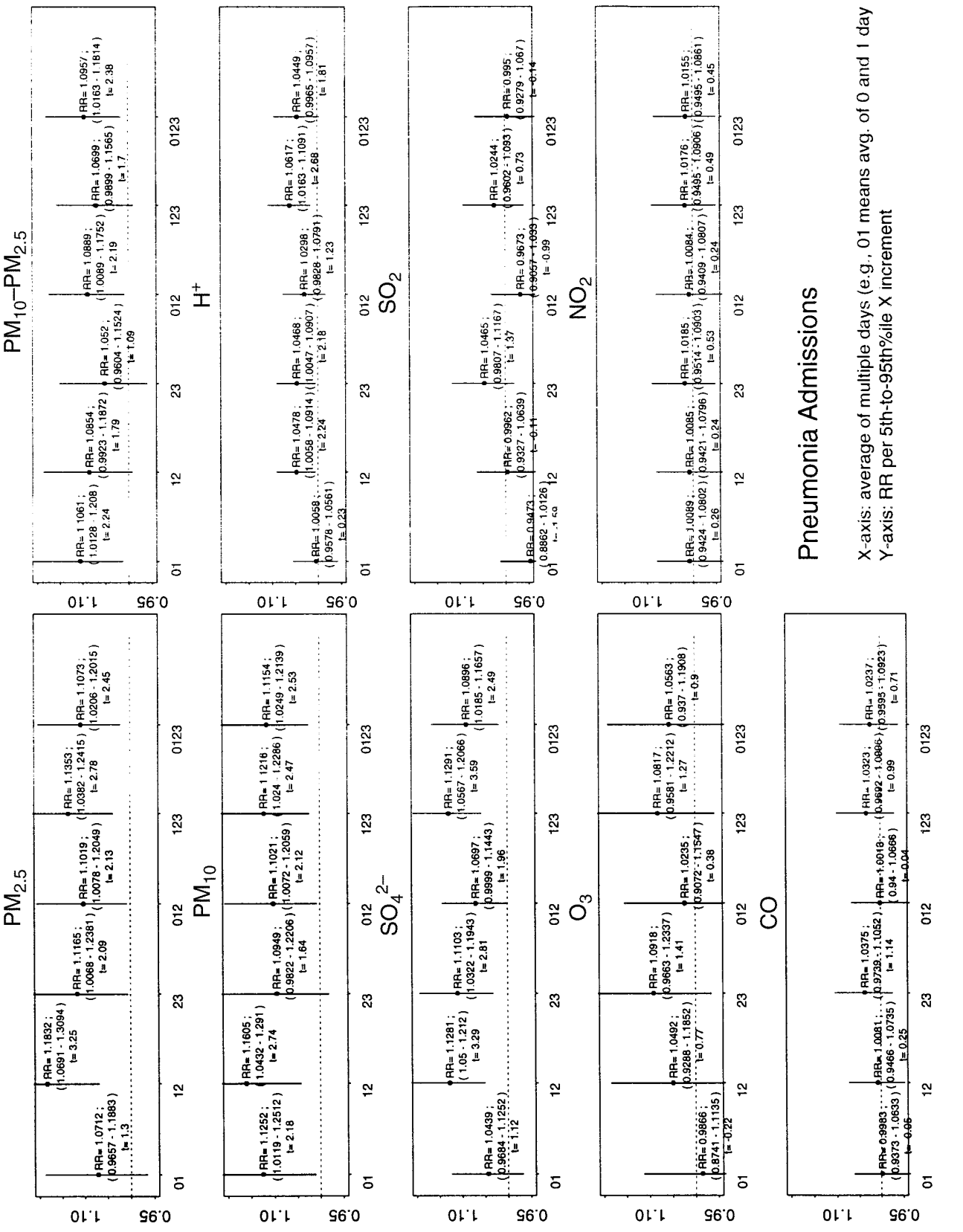

PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Stroke Admissions
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

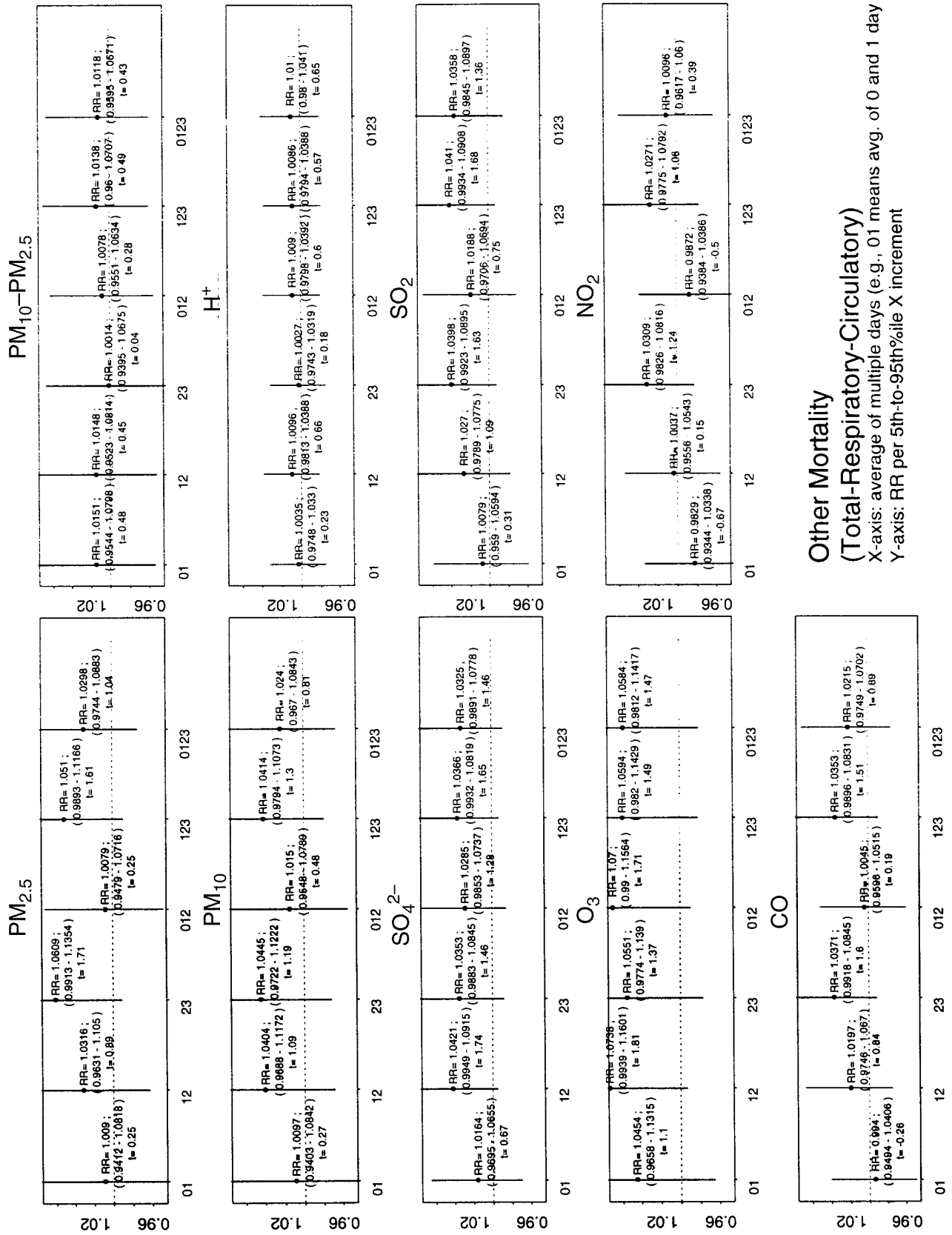

PM2.5
PM10
SO4 2−
O3
CO
PM10–PM2.5
H+
SO2
NO2
Heart Failure Admissions
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

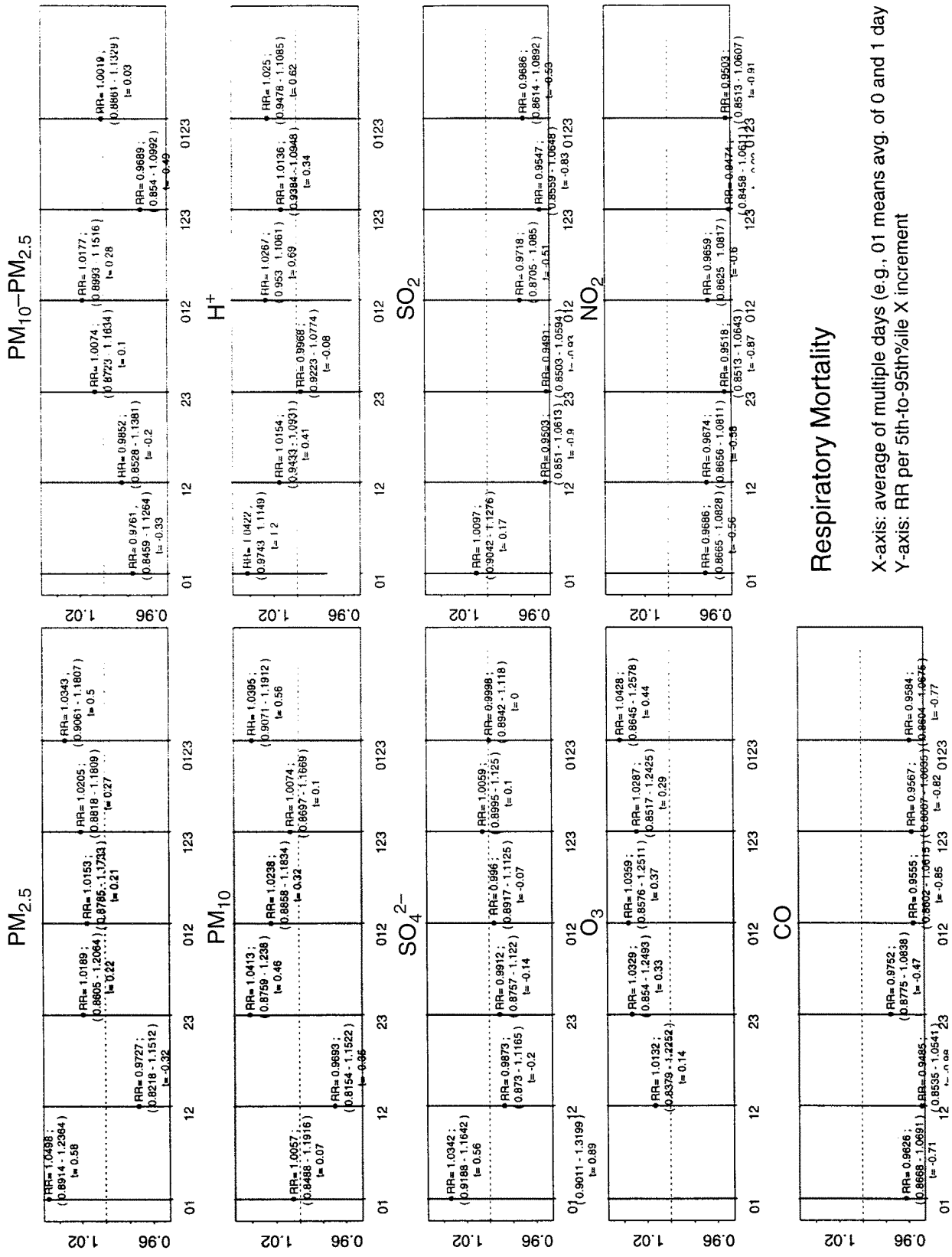

PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Dysrhythmia Admissions
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

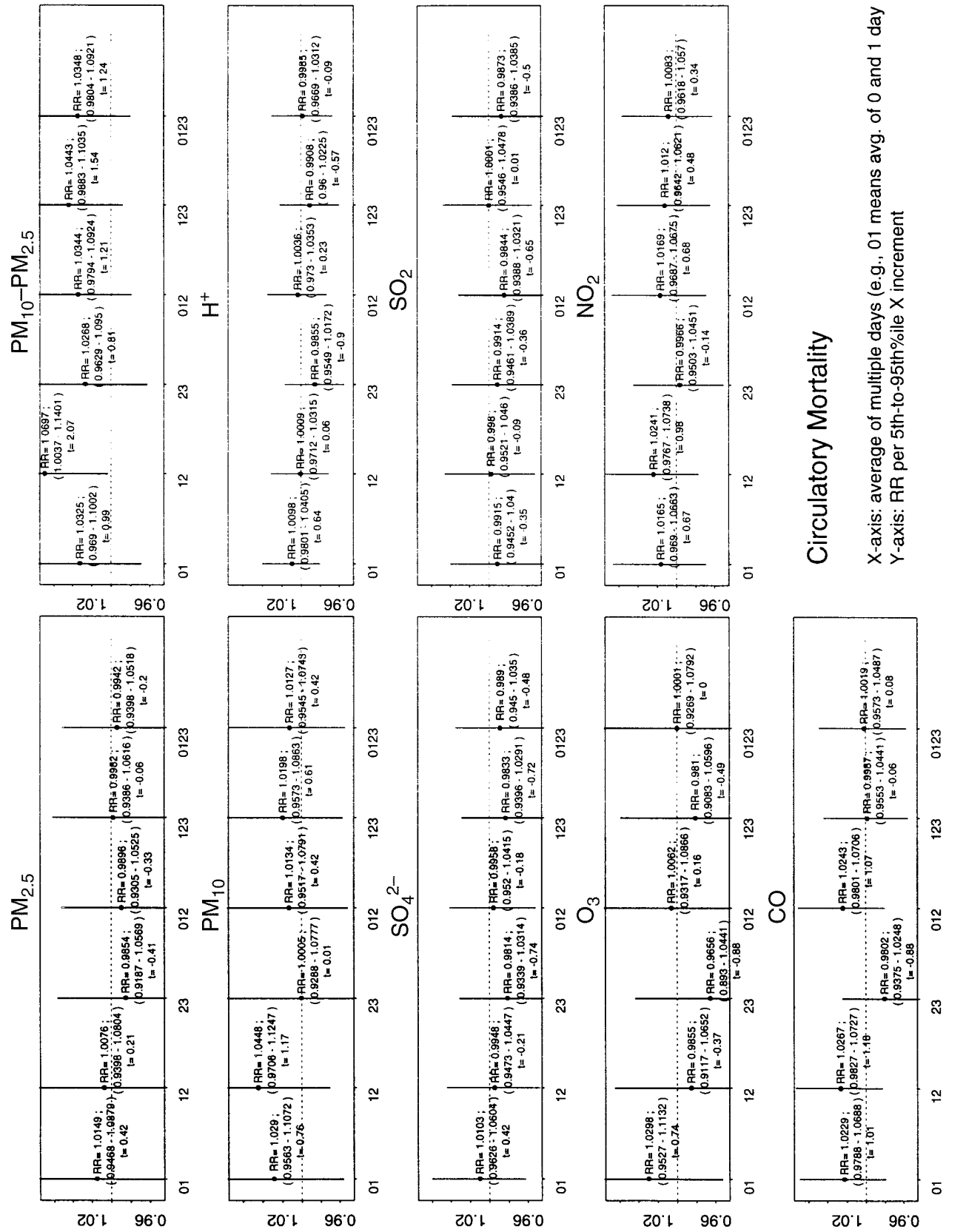

PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Ischemic Heart Dis. Adms.
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

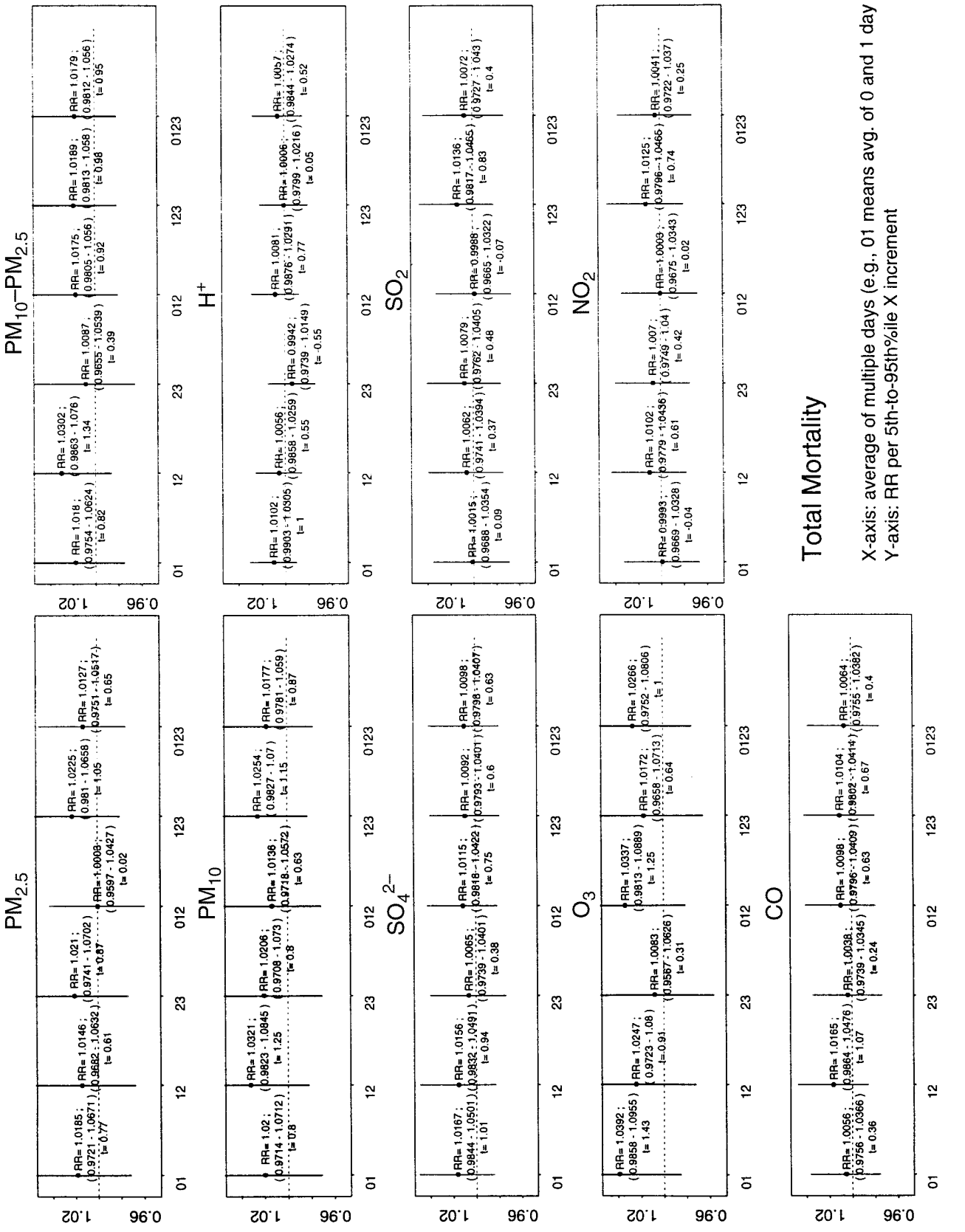

PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
COPD Admissions
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

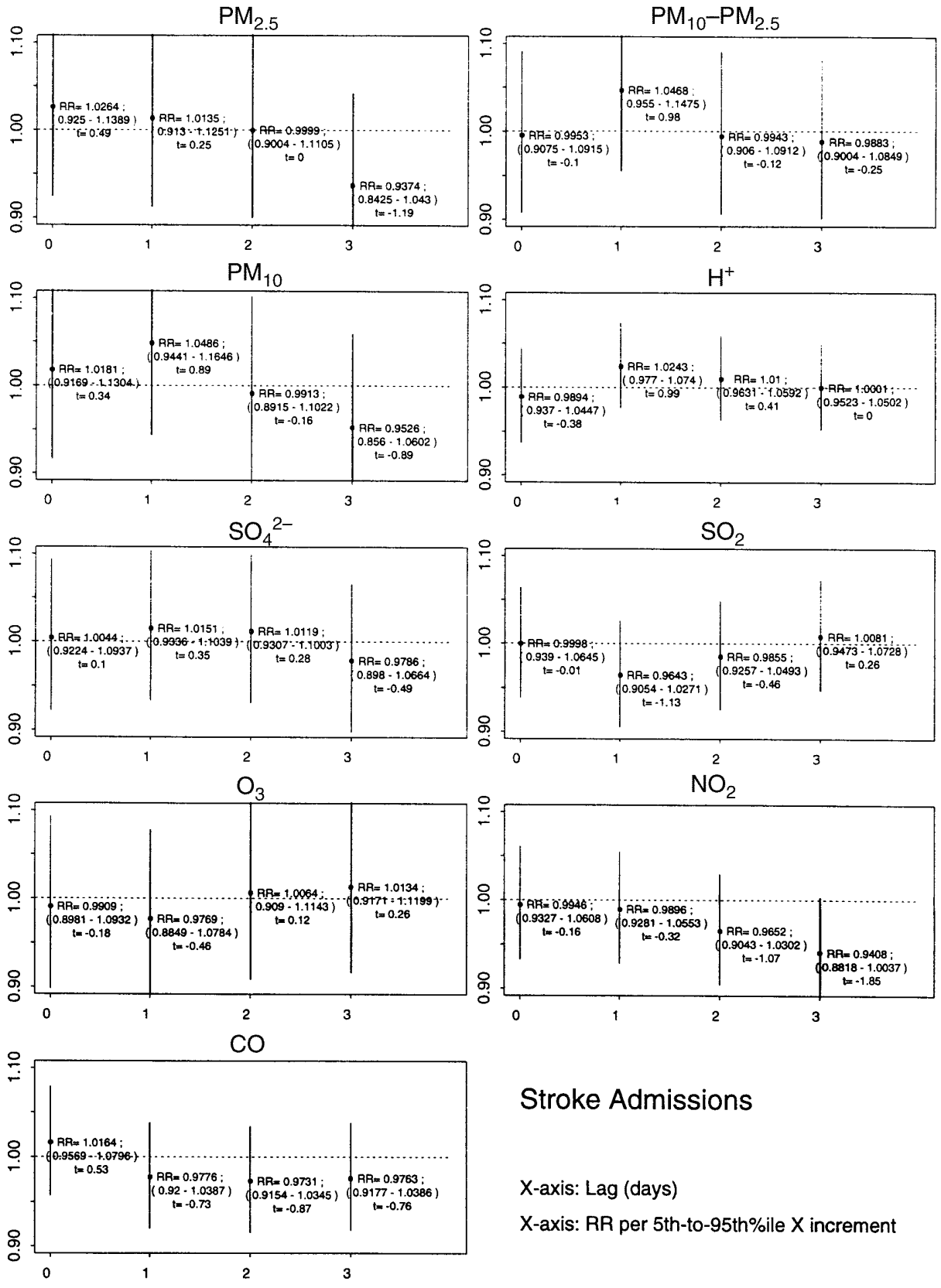

PM2.5
PM10
SO4 2−
O3
CO
PM10–PM2.5
H+
SO2
NO2
Pneumonia Admissions
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment


PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Other Mortality
(Total-Respiratory-Circulatory)
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment


PM2.5
PM10–PM2.5
PM10
H+
SO4 2–
SO2
O3
NO2
CO
Respiratory Mortality
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment


PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Circulatory Mortality
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment

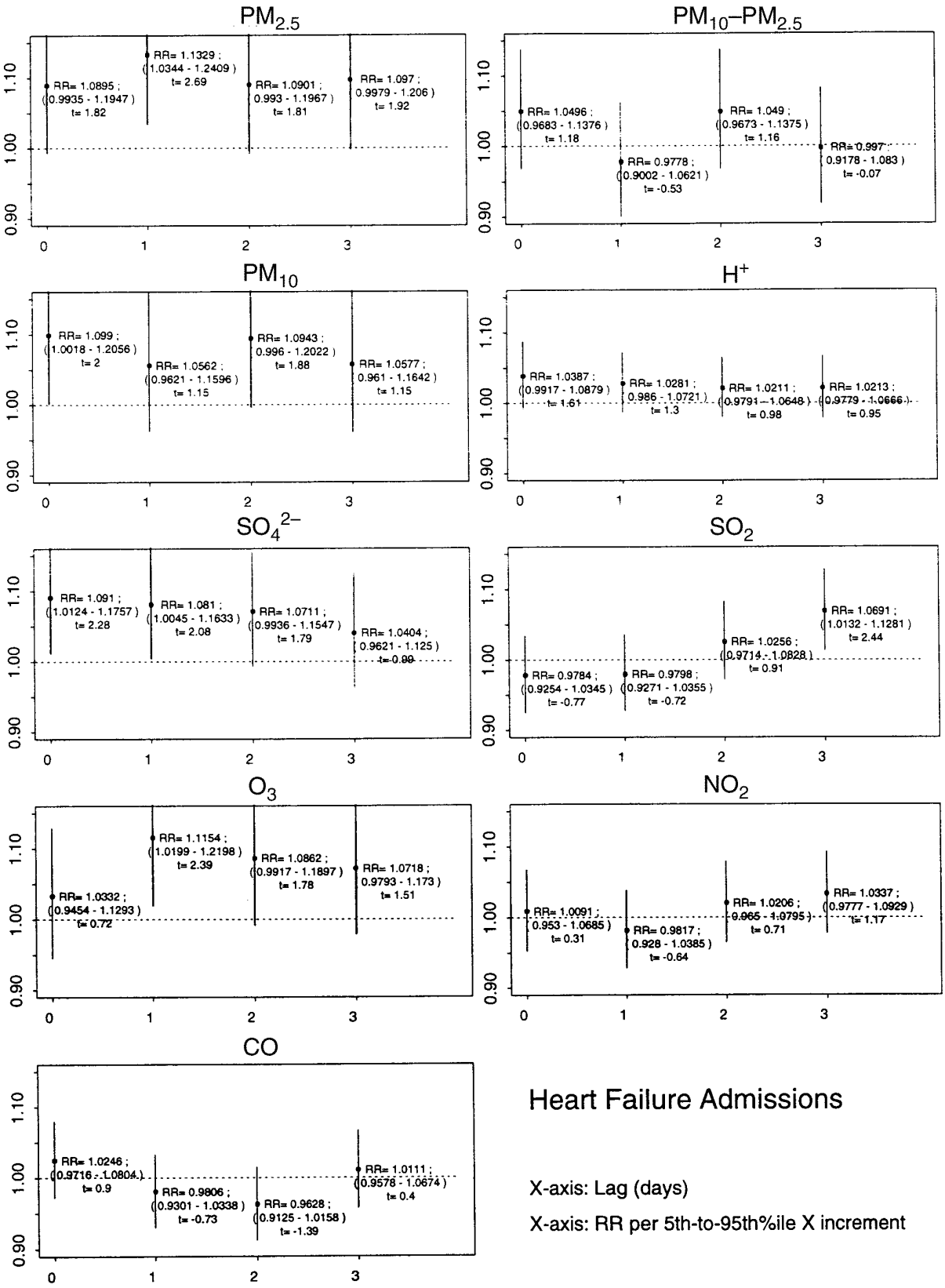

PM2.5
PM10
SO4 2−
O3
CO
PM10−PM2.5
H+
SO2
NO2
Total Mortality
X-axis: average of multiple days (e.g., 01 means avg. of 0 and 1 day
Y-axis: RR per 5th-to-95th%ile X increment



Stroke Admissions

X-axis: Lag (days)

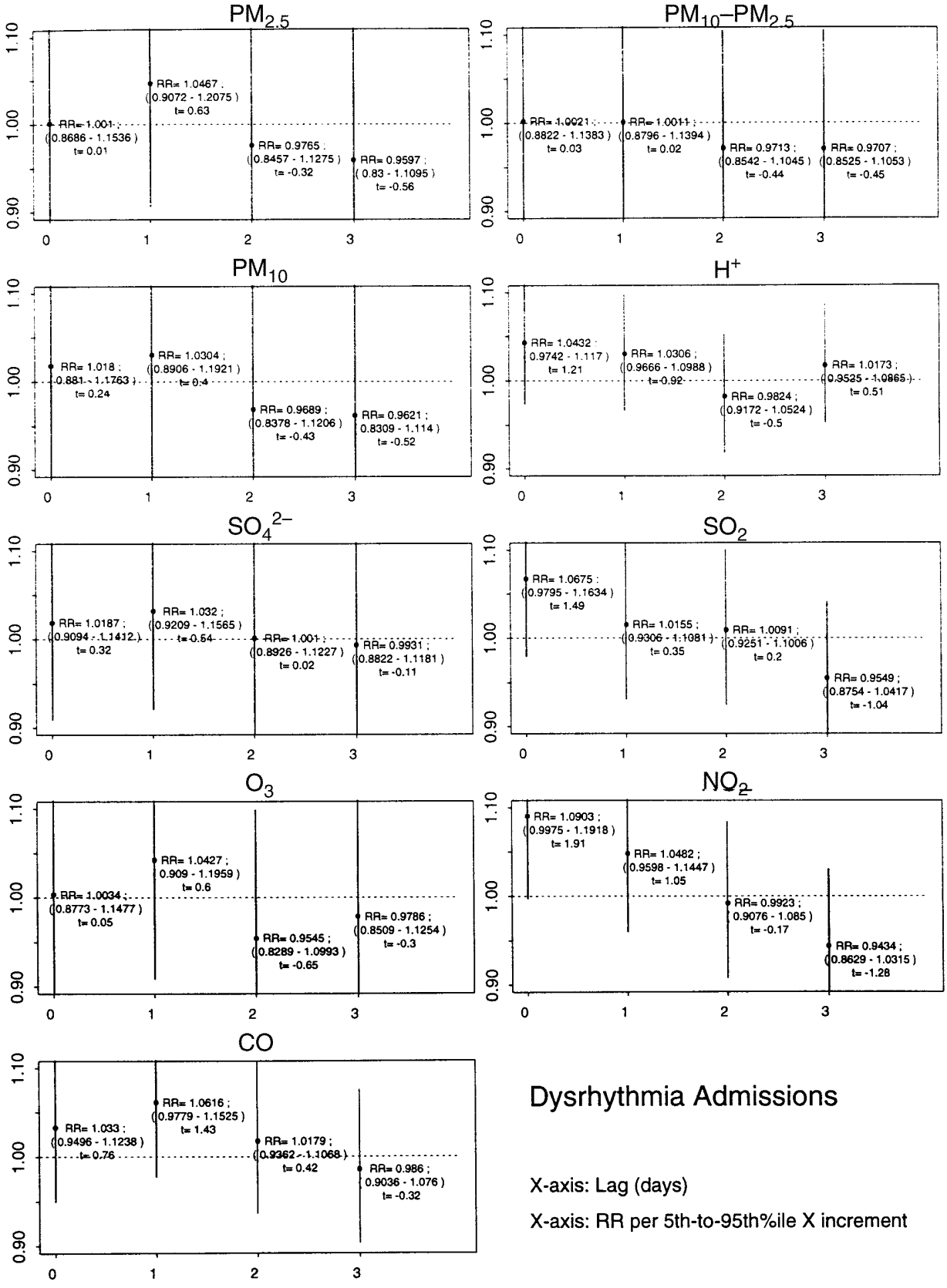
X-axis: RR per 5th-to-95th%ile X increment



Heart Failure Admissions

X-axis: Lag (days)

X-axis: RR per 5th-to-95th%ile X increment



Dysrhythmia Admissions

X-axis: Lag (days)

X-axis: RR per 5th-to-95th%ile X increment

APPENDIX E. HEI Quality Assurance Report

The conduct of this study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of an auditor with experience in toxicology and epidemiology and a practicing board certified physician epidemiologist. The audits included in-process monitoring of study activities for conformance to the study protocol and examination of records and supporting data. The dates of each audit are listed in the table below with the phase of the study examined:

Quality Assurance Audits

Date	Phase of Study Audited
May 8–9, 1997	The auditors reviewed the Data Processing Quality Assurance Guidelines (1/11/97), the original grant proposal, and the Year 1 Ten Month Progress Report (5/5/97). Acquisition and handling of the air quality, weather, Health Canada, and HCFA databases were investigated. Procedures for data processing, organization of database files, and archiving were audited. The current status of the project was assessed. Staffing, adequacy of computer equipment and facilities, and internal quality assurance procedures were considered.
Nov 9–10, 1998	The auditors reviewed the Study Protocol (12/1/97) and the Year 2 Ten Month Progress Report (7/12/98). Procedures for data storage and maintenance of confidentiality were considered. Archiving of data in accordance with HCFA requirements was verified. Staffing, equipment, and facilities considered in the first audit were reviewed. The current status of the project, in relationship to the Study Protocol, was clarified. The auditors reviewed the one-page Documentation of Study Purpose and Objectives.
Aug 14–15, 2000	The final report dated December 21, 1999, was audited against data processing diagrams and the printouts from the data analysis. The auditors compared information as presented in the tables to summary data presented in the analysis printouts. The auditors also compared the information in the Results section of the report to data contained in the tables and figures.

Written reports of each inspection were provided to the Director of Science of the Health Effects Institute who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by experienced professionals in accordance with the Documentation of Study Purpose and Objectives. The report appears to be an accurate representation of the study purpose and objectives and of the data that were audited.

B Kristin Hoover, Audit Coordinator

ABOUT THE AUTHORS

Morton Lippman is Professor of Environmental Medicine at New York University School of Medicine. He is also Director of the Human Exposure and Health Effects Research Program of the Department of Environmental Medicine and the Particulate Matter Health Effects Research Center at NYU supported by grant R827351 from the US Environmental Protection Agency. He received a BChE from the Cooper Union in 1954, an SM in industrial hygiene from Harvard University in 1955, and a PhD in environmental health science from NYU in 1967. His research interests focus on exposure assessment and the health effects of airborne toxicants.

Kazuhiko Ito received his PhD in environmental health science at NYU's Institute of Environmental Medicine, where he is currently assistant professor. His interests are air pollution epidemiology and exposure analysis.

Arthur Nádas received his PhD in mathematical statistics at Columbia University. For many years, he worked in statistical software development at IBM Corporation, where he also worked on speech recognition. Dr Nadas is currently a faculty member at NYU's Institute of Environmental Medicine. His interests focus on biostatistics.

Richard T Burnett received his PhD in mathematical statistics from Queen's University in 1982. He is a senior research scientist with the Environmental Health Directorate of Health Canada, where he has been working since 1983 on issues relating to the health effects of outdoor air pollution. Dr Burnett's work has focused on the use of administrative health and environmental information to determine the public health impact of combustion-related pollution using

nonlinear random effects models, time series, and spatial analytic techniques.

ABBREVIATIONS AND OTHER TERMS

AIC	Akaike Information Criterion
AIRS	Aerometric Information Retrieval System
BS	black smoke
CI	confidence interval
CMSA	Consolidated Metropolitan Statistical Area
CO	carbon monoxide
COH	coefficient of haze
COPD	chronic obstructive pulmonary disease
df	degrees of freedom
EPA	US Environmental Protection Agency
GAM	generalized additive models
H^+	particle acidity
H_2SO_4	sulfuric acid
HCFA	Health Care Financing Administration
ICD-9	*International Classification of Diseases, Ninth Revision*
LOESS	locally weighted smoothing scatterplots
MEDPAR	Medical Provider Analysis and Review
MSA	Metropolitan Statistical Area
NCDC	National Climatic Data Center
NCHS	National Center for Health Statistics
PM	particulate matter
$PM_{2.5}$	particulate matter 2.5 μm or less in aerodynamic diameter
PM_{10}	particulate matter 10 μm or less in aerodynamic diameter
$PM_{10-2.5}$	PM_{10} minus $PM_{2.5}$ (an estimate of particulate matter ≤ 10 μm and ≥ 2.5 μm in aerodynamic diameter)
RR	relative risk
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
TSP	total suspended particles
TSP–PM_{10}	TSP minus PM_{10}
TSP–SO_4^{2-}	TSP minus SO_4^{2-}
WBAN	Weather Bureau, Air Force, and Navy

INTRODUCTION

Many epidemiologic studies in areas with different topography, weather, and other characteristics have reported an association between daily fluctuations in the levels of ambient particulate matter (PM)* and changes in mortality and morbidity. These effects have been reported in areas with generally low PM levels as well as areas with high average PM levels. In urban and other environments, however, PM is not a single physical or chemical entity but rather a mixture of particles of various sizes, shapes, and compositions. Relatively few studies have addressed which components of this mixture are responsible for the reported associations.

Limited epidemiologic evidence suggests a stronger association with increased mortality and morbidity for fine particles, less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), than for larger particles, up to 10 μm in diameter (PM_{10}). Instruments that measure particle mass up to the upper end of the range include the lower end as well, however, because by definition, PM_{10} contains $PM_{2.5}$. Thus, differentiating their effects is difficult. Particles of different sizes may have different effects on human health: more of $PM_{2.5}$ can enter the deep lung; while coarse thoracic particles, more than 2.5 μm in diameter and less than 10 μm in diameter ($PM_{10–2.5}$) are deposited primarily in the larger air passages of the upper respiratory tract. Understanding which particles are more toxic is important because appropriate control strategies to reduce the particles may differ substantially according to their size and composition.

The US Environmental Protection Agency (EPA) regulations for PM mass are based on particle size measured as aerodynamic diameter. This measure depends on particle density and is defined as the diameter of a particle with the same settling velocity as a spherical particle with a material density of 1 $\mu g/cm^3$. From 1971 to 1987, the National Ambient Air Quality Standards (NAAQSs) regulated PM using the measurement of total suspended particles (TSP), which includes all particulate matter up to 40 μm in diameter. Currently, the EPA maintains NAAQSs for, and regulates the ambient levels of, PM_{10} and $PM_{2.5}$, which when inhaled penetrate to the upper respiratory tract and deep lung, respectively. Primary NAAQSs (to protect human health) were set for PM_{10} at 150 $\mu g/m^3$ averaged over 24 hours and at 50 $\mu g/m^3$ averaged over 1 year (EPA 1987). In 1997, the EPA added standards for $PM_{2.5}$, with the 24-hour standard at 65 $\mu g/m^3$ and the annual standard at 15 $\mu g/m^3$ (EPA 1997). The European Union adopted similar limit values for PM_{10} and is considering whether to regulate also $PM_{2.5}$. Dr Lippmann and colleagues' research was designed to assess whether the effects of PM on daily mortality and morbidity depend on the size and composition of the particles, and whether other pollutants interact with PM to alter its effects.

In the summer of 1994, HEI issued a request for preliminary applications (RFPA 94-3) for studies of the health effects of exposure to motor vehicle emissions. In response, Morton Lippmann of New York University submitted a preliminary application, which was a revised version of an earlier proposal submitted in response to RFA 94-2 "Particulate Air Pollution and Daily Mortality: Identification of Populations at Risk and Underlying Mechanisms." The first objective of RFA 94-2 was to identify populations at increased risk of mortality from particles and the conditions of pollutant exposure and other factors that are associated with increased mortality. On the basis of the preliminary application, the Health Research Committee requested a full application, which Dr Lippmann submitted in November 1995. He proposed a 3-year study of daily deaths and hospital admissions in relation to air pollution using publicly available databases on health outcomes in Detroit and air monitoring data from Detroit and its close neighbor Windsor, Ontario.†

BACKGROUND

THE AMBIENT PARTICULATE MATTER MIXTURE

Particulate matter refers to a mixture of chemically and physically diverse particles (solid or liquid) in a range of sizes: ultrafine particles (less than 0.1 μm in diameter); fine particles ($PM_{2.5}$, which includes the ultrafine particles); and coarse particles evaluated in this study using ($PM_{10–2.5}$). Ultrafine particles derive primarily from combustion processes and tend to form fine particles either by

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† Dr Morton Lippmann's 3-year study, *Association of Particulate Matter Components with Daily Mortality in Urban Populations*, began in June 1996 with total expenditures of $352,500. The Investigators' Report was received for review in September 1999. A revised report, received in December 1999, was accepted for publication in February 2000. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Health Review Committee's Commentary.

agglomeration or by the condensation of volatile material on them. This process usually occurs within a few minutes of their emission into the air. Fine and ultrafine particles are produced by emissions from combustion processes, while most coarse particles are generated by mechanical processes.

Generally, the ultrafine and fine fractions of PM are composed of carbonaceous material, metals, sulfate, nitrate, and ammonium. The coarse fraction is composed mostly of insoluble minerals (wind-blown dusts) and biologic aerosols, with smaller contributions from primary and secondary aerosols and sea salts. Particulate matter is called primary if emitted directly from sources and secondary if formed in the atmosphere. Secondary PM can form by chemical reactions with gases such as sulfur oxides, nitrogen oxides, volatile organic compounds, and many elements that are associated with it in the atmosphere (lead, selenium, arsenic, etc). Understanding how different sources contribute to atmospheric particle levels and how different particles contribute to health effects is important for designing a rational control strategy.

EPIDEMIOLOGY

When the application for the current study was submitted in 1994, most of the information from time-series studies about the association between daily mortality and size-fractionated PM was based on PM_{10}, with some studies looking at black smoke (Ministry of Health 1954), TSP (Schwartz 1991), sulfate (Thurston et al 1992; Dockery et al 1993; Delfino et al 1994), and particle strong acidity, reflected by the presence of hydrogen ions (H^+) (Thurston et al 1989, 1992; Ito et al 1993). A series of hospital admissions studies in Canada and the United States evaluated PM_{10} or $PM_{2.5}$ (Bates and Sizto 1983, 1987; Thurston et al 1992, 1994; Burnett et al 1994; Schwartz 1994). Overall, studies of hospital admissions for both chronic obstructive pulmonary disease (COPD) and pneumonia showed moderate associations with PM_{10}. Although most persons hospitalized for respiratory illness are 65 years or older, some are younger. Few hospital admissions studies have looked at this younger group, though Pope (1991) reported that monthly hospitalization rates of preschool children in Utah Valley were correlated with monthly averages of PM_{10}. In long-term prospective studies, Dockery and colleagues (1993) and Pope and coworkers (1995) found $PM_{2.5}$ and sulfate (SO_4^{2-}) were associated with mortality. Sulfate was found to be predictive of health effects; however, there was no clear delineation of the effects of the acidity of SO_4^{2-}, and it was not clear whether the effects of SO_4^{2-} could be due to its broader relationship to combustion-related $PM_{2.5}$. In summary, studies thus far have not revealed a consistent pattern to suggest a ranking among PM constituents in significance of associations with health outcomes.

TECHNICAL EVALUATION

AIMS AND OBJECTIVES

The overall objective of the study was to identify the PM components that are associated with excess daily deaths and hospital admissions in the elderly. This was assessed using the relative risk (RR), which is the relative increase in experiencing an adverse outcome (death or illness) given the presence of some risk factor (air pollutant), calculated for an increment in each air pollution variable equal to the difference between the 5th and 95th percentiles of their distributions. The study had two specific objectives. One was to investigate the relative contributions of specific PM components to daily mortality and morbidity, including the effects of TSP, PM_{10}, particles less than 40 μm and greater than 10 μm in diameter (TSP–PM_{10}), $PM_{2.5}$, $PM_{10-2.5}$, sulfate without sampling error (artifact-free SO_4^{2-}), sulfate from TSP (TSP–SO_4^{2-}), and H^+. The other objective was to investigate three issues important in interpretation of time-series analysis of multiple air pollutants: the relative spatial variability of air pollutants; the effect of choice of PM monitoring site on the estimated relative risk of mortality; and the influence of multiple admissions for a single individual on relative risk of hospital admissions.

STUDY DESIGN

Dr Lippmann and colleagues conducted several time-series analyses to estimate the effect of daily changes in ambient air pollution on daily rates of mortality and morbidity in the Detroit metropolitan area. The study used existing data from the EPA's Aerometric Information Retrieval System (AIRS) and from Environment Canada. The investigators used Poisson (log-linear) regression models to estimate the effects of individual PM components and the gaseous pollutants sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) on daily deaths from all nonaccidental causes, circulatory causes, respiratory causes, and nonaccidental minus circulatory and respiratory causes, and on daily hospital admissions for the elderly population (65 years or older) for pneumonia, COPD, ischemic heart disease, dysrhythmias, heart failure, and stroke.

Four sets of analyses comprised the study:

1. Relative risk estimation of daily mortality in relation to size-fractionated PM mass (TSP, PM_{10}, TSP–PM_{10}, TSP–SO_4^{2-}) and gaseous pollutants (SO_2, NO_2, O_3, and CO) for the period 1985–1990 in the Detroit metropolitan area (Wayne County, Michigan);
2. analysis of the association of both mortality and morbidity with PM components (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, H^+, and SO_4^{2-}) and gaseous pollutants (SO_2, NO_2, O_3, and CO) for the period 1992–1994 in the Detroit metropolitan area;
3. evaluation of the sensitivity of PM-mortality associations in the Detroit metropolitan area to choice of 14 TSP monitoring sites for the period 1981–1987; and
4. estimation of the effects of ambient air pollution on hospital admissions among the elderly in a larger geographic area (the Detroit–Ann Arbor–Flint Consolidated Metropolitan Statistical Area), from 1992 to 1994.

The extent to which pollutant concentrations increased and decreased together was estimated by calculating pairwise Pearson correlation coefficients. Correlation coefficients were calculated for each pair of PM and gaseous air pollutant metrics, for the periods of 1985–1990 and 1992–1994. To investigate the extent to which a single pollutant level varied across location, correlation coefficients were also calculated for the same pollutant sampled at any two different sites, for the period 1981–1994. Factor analysis, a statistical technique designed to identify underlying sources of many highly correlated variables, was used to assess the correlations among PM metrics, gaseous pollutants, and weather variables.

METHODS

Air Pollution Data

The investigators used two nonoverlapping sources of air pollution data. In addition to the EPA's AIRS data available from several monitoring stations in Detroit, aerosol measurements were available from two Canadian stations across the Detroit River, in Windsor, Ontario. One-hour average values of the gaseous measurements (SO_2, NO_2, O_3, and CO) were available from AIRS for 1981–1994; O_3 data were collected only in the warm season (April to October) from fall 1988 on. Meteorologic data came from a station at the Detroit Metropolitan Airport.

Mortality and Morbidity Data

Daily death counts for were obtained for Wayne County, Michigan were obtained from the National Center for Health Statistics. Accidental deaths and deaths that occurred outside the county of residence were excluded. In addition to total mortality, deaths were separated into three mutually exclusive categories: deaths due to circulatory problems, deaths due to respiratory diseases, and all other nonaccidental deaths (total minus respiratory and circulatory). Hospital admission data for persons aged 65 and older were obtained from Medicare files of the State of Michigan Health Care Financing Administration (MEDPAR hospital discharge files). Only admissions classified as "emergency" and "urgent" were selected, in order to examine acute effects of air pollution. Asthma admissions were not included, partially because there were few of them, and partially because of the tendency for asthma in the elderly to be misdiagnosed as other COPDs.

Regression Analyses of Mortality and Morbidity

The statistical models for daily mortality were developed sequentially, first modeling longer-term trends in mortality (due to season, influenza epidemics, day-of-week, etc), then adding terms for weather (temperature and relative humidity). These adjustments were done separately for the deaths due to respiratory diseases, compared with total deaths and deaths due to circulatory diseases. The choice of variables and their specification were guided both by prior knowledge of biological plausibility and by statistical criteria (statistical significance of the relative risks, goodness of fit of the model to the data based on Akaike Information Criterion, and reduction in overdispersion relative to the Poisson error model). After fitting the basic model, air pollution variables were added.

The timing of the effect of air pollution can be estimated from daily time-series data. The relative timing of effects was evaluated by examining pollutant levels on successive days, a so-called lagged analysis. For example, the relative risk of mortality was estimated for exposure on the day of death (lag 0), the previous day (lag 1), 2 days before death (lag 2), and 3 days before death (lag 3). For each air pollutant metric (PM or gas) the best lag was decided post hoc; ie, the lag identified as best had the largest positive relative risk. Cumulative effects were evaluated by averaging the effect over multiple lag days (0- through 3-day lags were examined). The results for all single-day lags and multiple-day average lags are presented in Appendix C (1985–1990) and Appendix D (1992–1994).

Time-Series Analyses of Multiple Air Pollutants

Issues Important in Interpretation of Relative Spatial Variability of Air Pollutants The time-series analyses in this report investigate the relationship between an air pollutant

and a health outcome. However, air pollutants and people are distributed in space as well as time. Air pollutants can be distributed uniformly or variably in space. Therefore, the authors investigated the spatial distribution of a single air pollution index (PM_{10}, TSP, SO_2, NO_2, CO, and O_3) across many sites for all available days between 1981 and 1994. Longitude and latitude were used to calculate the distance between monitoring sites. Then, the authors examined the correlations of each pollutant from each pair of monitoring sites relative to the distance between sites. Finally, the authors calculated the median of all the correlation coefficients for all the pairs of monitoring sites, by pollutant. This median correlation, calculated site-to-site, was used to evaluate "spatial uniformity" for each individual air pollutant (PM metrics and gaseous pollutants). This analysis could not be conducted for variables that did not have multiple monitoring stations ($PM_{2.5}$, H^+, and SO_4^{2-}).

The extent to which concentrations of the different pollutants were correlated was estimated by calculating pairwise Pearson correlation coefficients. To investigate the extent to which PM and gaseous pollutants were correlated, correlation coefficients were calculated for each pair of different air pollutants, for the periods of 1985–1990 and 1992–1994. The correlations among PM metrics, gaseous pollutants, and weather variables were also explored using factor analysis.

Effects of Monitoring Site on Estimated Relative Risk of Mortality The authors identified 14 TSP monitoring sites operated from 1981 to 1987 no major fraction of missing data (the authors did not specify their criterion). The total (nonaccidental) mortality model developed for 1985–1990 was used to calculate relative risk for each of the 14 sites, for lags of 0 through 3 days. The authors used graphs to describe the pattern of relative risks for each lag period (0 to 3 days) and each monitoring site.

Influence of Multiple Admissions on the Estimated Pollution Risks Repeated hospital admissions of a small number of patients could distort the apparent association between air pollutants and morbidity by artificially inflating the overall number of admissions (independent variable) when the level of air pollutant (dependent variable) did not change. For the period 1992–1994, the investigators assessed effects of multiple hospital admissions on the estimated PM_{10} relative risks. Separate time series analyses were used to compare the relative risks for persons with multiple hospital admissions and persons with one hospital admission.

Factor Analysis Factor analysis was used to study patterns of correlations among PM metrics and gaseous pollutants. This statistical tool, which is especially useful for investigating relationships between numerous highly correlated measurements, was used to investigate how the PM metrics, gaseous pollutants, and weather variables change together. The statistical technique is designed to convert multiple, highly correlated variables to a reduced number of uncorrelated linearized sums, or vectors, referred to as factors. The reduced number of factors retain nearly all of the original information, but are not correlated with each other. Factor loadings represent correlations between each independent variable (air pollutant) and an individual factor (possible source of the air pollutant). Because the technique identifies air pollutants that group together, a factor may represent the source of a group of pollutants, and the pattern of loadings observed for an individual factor might be used to identify such underlying sources, which could in turn assist regulatory efforts to protect human health.

RESULTS

1985–1990 Mortality

In single-pollutant models the authors reported increased relative risks for respiratory causes of death. For example, for increase of 76 $\mu g/m^3$ in PM_{10} they reported a relative risk at lag 1 of 1.123 (95% confidence interval [CI]: 1.0361, 1.218), with similar values at other lags (see Appendix C). The estimated relative risks did not change appreciably when multiple-day averages were substituted for individual-day lags. In two-pollutant models that included PM and one gaseous pollutant, the association of PM_{10} with respiratory mortality was apparently reduced only when O_3 (at lag 2) was included (95% CI: 1.123, 1.080; see Table 7). In general, the associations with the various pollutants were much smaller for total, circulatory, and other causes of mortality (relative risks less than 1.05) than for respiratory mortality.

Ozone and NO_2 were also significantly associated with total and circulatory mortality. However, simultaneous consideration of PM_{10} with these pollutants reduced PM_{10} coefficients only slightly, or even increased them.

1992–1994 Mortality and Morbidity

The authors reported that all three of the PM mass indices, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$, showed similar associations with mortality. The H^+ and SO_4^{2-} associations with mortality were closer to unity (1.0), although the lack of results could be due to the low acidity (H^+) levels, which were below the detection limit on most study days. The

authors point out in their conclusions and abstract that this result is not consistent with their original hypothesis regarding the role of acidity in the air pollutant–mortality relationship. Although few of the relative risks for mortality were statistically significant (ie, the results could have occurred by chance alone), the authors had to restrict their analyses to the study period when H^+ and SO_4^{2-} data were available. Without this restriction, the PM mass indices were significant for total mortality, circulatory mortality, COPD admissions, and ischemic heart disease admissions, without notable difference in the relative risks.

The authors reported that each of the PM mass indices (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) was associated with an estimated increase in the rate of hospital admissions of about 10% for COPD, ischemic heart disease, and heart failure admissions, and about 20% for pneumonia admissions, with slightly different estimates for various single-day lags and several different combinations of days (averages) over the previous 3 days (Appendix D). These relative risks of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were associated with a concentration range (5^{th} to 95^{th} percentile) of 51 $\mu g/m^3$, 36 $\mu g/m^3$, and 24 $\mu g/m^3$, respectively. As in the mortality analyses discussed above, the inclusion of O_3 (at lag 3) resulted in an appreciable change in the $PM_{2.5}$ relative risk (for pneumonia; see Table 16).

The authors observed that $PM_{2.5}$ and $PM_{10-2.5}$ were complementary size-fractionated components of PM_{10} and only moderately correlated in this data set, and they included both of these PM metrics in regression models (Figure 18). In most cases, the coefficients for models with $PM_{2.5}$ and $PM_{10-2.5}$ were lower than those for models with only one PM metric.

1992–1994 Multiple Hospital Admissions

The investigators recognized that repeated hospital admissions could be an important aspect of any association between air pollutants and morbidity. For the period 1992-1994, the investigators assessed the effects of multiple hospital admissions on the estimated relative risks for PM_{10}. Separate time-series analyses were used to compare the relative risks for persons with multiple hospital admissions and persons with one hospital admission. For pneumonia, a diagnosis for which repeated admissions during the 3-year time period were relatively unusual (1.17 mean admissions per subject), the effect estimates did not differ. However, for COPD, a diagnosis for which repeated admissions were more common (1.58 mean admissions per subject), effect estimates were smaller for persons with more than one hospitalization than for those with only one hospitalization. This empiric evaluation suggested that the effect of including those with multiple admissions in the analysis was, if anything, conservative, and tended to produce smaller effect estimates.

Another relevant issue is that multiple admissions, by definition, create data that are not independent, which affects the validity of the effect estimate variances, which, in turn, affects tests of statistical significance. Generally, use of nonindependent data tends to result in underestimation of variance, which overestimates statistical significance, a nonconservative outcome. The impact of this effect on estimate variance in this study is not known, but the results of the sensitivity analysis that examined the subset of subjects with only one admission, and for which data are therefore independent, would also be useful here. Unfortunately, the stratification of the admissions that this approach entails reduces the power in each stratum, which would also influence the variances of the effect estimates.

Environmental Measurements Characterization

Spatial Characterization For studies of air pollution and human health, it is important to know whether the values of an air pollutant are constant over space. To address this question, the investigators looked at the correlation for each pollutant across several sampling locations. Median site-to-site correlation was highest for O_3 ($r = 0.83$), PM_{10} ($r = 0.78$), and TSP ($r = 0.71$). In general, these three pollutants with the highest spatial uniformity in daily fluctuations were associated with the largest relative increases in mortality in the Detroit time-series study. Correlations between PM metrics and gaseous pollutants were generally around 0.50.

Factor analysis was used to identify a "summer haze" factor and a "primary pollution" factor, which were not well defined or discussed. The authors noted that the coarse fraction, $PM_{10-2.5}$, had its own factor, suggesting that $PM_{10-2.5}$ was uncorrelated with the other PM indices.

In the Detroit metropolitan area, for the years included in this study, $PM_{2.5}$ accounted for, on average, 60% of PM_{10} (and up to 80% on some days); PM_{10}, on average, accounted for 66% of TSP mass (Figure 10).

Choice of PM Monitoring Sites The authors used the TSP data for 1981–1987 to investigate the effect of choice of PM monitoring sites on the main analyses. They reported that the relative risks estimated for TSP were not sensitive to choice of site, and that TSP measurements for the Windsor site were a reasonable proxy for sites in the Detroit metropolitan area.

DISCUSSION

The primary goal of the study was to identify and characterize the air pollutants that were most strongly associated with daily deaths and hospital admissions in the Detroit area. However, in the current study the relative risks are small, their confidence intervals overlap, and their relative magnitudes cannot be estimated with precision. Therefore, the results do not show a clear pattern of comparatively larger effect for any of the PM metrics.

More globally, several issues inherent to epidemiologic time-series studies may interfere with interpretation of relative effects among air pollutants. Separation of the effects of one pollutant from those of others can be extremely difficult owing to the collinearity of pollutants; that is, humans are exposed to highly correlated mixtures of PM, copollutants, and other unmeasured pollutants. Also difficult to separate out is the temporal variation in pollutant-mortality associations, whether effects are being observed on the same day, or whether there is a lag pattern in the data of 1, 2, 3, or more days from the measurement of air pollutant levels until the health endpoint. Estimated effects can change with—or exhibit sensitivity to—different analytical approaches, multiple-pollutant models, or susceptible subpopulations. However, the estimation of effects of many pollutants over several lag periods and for different models can result in some significant associations being observed by chance alone due to multiple testing. Typically for these epidemiologic studies, the use of a central monitoring site to evaluate exposure of a mobile human population can result in measurement error, that is, the error in assigning an individual's exposure level on the basis of measurements by instruments some distance away from the individual. Finally, values of the air pollution data can be dependent on the results of different sampling techniques; for example, the measurements of sulfate from TSP may have added measurement error from the artifactual formation of SO_4^{2-} on the TSP glass-fiber filter.

Collinearity

A high degree of collinearity among major air pollutants is widely recognized as a serious problem in the interpretation of epidemiologic data. If mortality data are associated with each of a half-dozen pollutant indices, but the pollutants' levels tend to rise and fall together, it may be difficult or impossible to tell from the epidemiologic data alone whether the *cause* of the association with mortality or morbidity is some specific pollutant in the mixture, the mixture as a whole, or even some other, unmeasured component; pollutant indices could be reflecting mixture toxicity or component toxicity. Collinearity can create major problems in a multivariate analysis by making estimates of effect size highly unstable; in anthropomorphic terms, the model cannot make up its mind whether to attribute some effect to one of the correlated variables, another, or even sometimes their difference. This uncertainty is reflected in the results as highly unstable estimates of the effect attributed to each variable (that is, as large standard errors). Determination of cause is important because our understanding of cause affects our decisions about remedies, and remedies (engine redesign, smoke stack controls, etc.) that reduce a noncausal pollutant may produce little benefit at great cost. Thus, taking collinearity into account in exposures is an important goal in the epidemiology of air pollution.

Findings can be strengthened if the same general result (based on the full range of air pollutants) is found in multiple studies, and if cause-effect interpretations are also rooted in other kinds of investigations, such as laboratory studies. In short, collinearities add to the difficulties of drawing conclusions about causes and effects from observational data such as the authors present.

Multiple Testing

In the search for significant effects of air pollution on health (as for other matters), statistical analysis must be designed to guard against reporting that a relation exists when it is merely a reflection of chance variations in the data. This type of error, called Type I error, is controlled to the level specified in the familiar *P* values of ordinary statistical testing. Significance testing at the usual 5% level produces, on average, one statistically significant result for each 20 tests when no effect is present. Therefore, when numerous tests are performed, the chance of finding at least one statistically significant result when no effects are present may become quite large. This problem of multiple comparisons can be at least partially reduced by using more stringent critical values (for example, *P* less than 1%) and by looking for suggestive patterns in how the significant values are distributed across the data, including consideration of correlations among the various *P* values.

Lag Patterns in the Data

The authors present all of the lag results, including individual-day lags and an average effect for multiple days. However, the main findings reported for the study were dependent on choosing the best lag for each pollutant, and the lag was identified as best on the basis of the size of the estimated relative risk from the regression equation. Although many investigators of time-series studies have used this best lag approach, it has a potential to bias the results toward finding positive (or negative) statistically

significant associations. One example is the association between CO and circulatory mortality. Presentation of the best lag results for lag 1 (see Figure 15) does not show the paradoxically protective effect for lag 3 (see Appendix D).

The best lags approach was also used for the two-pollutant models assessing the effect of gaseous pollutants on PM metric coefficients; unlike the results for the PM metrics, only the best lags for the gaseous pollutants are presented, and the lags that gave the most significant coefficients varied. Presentation of all the lags for all the two-pollutant models would have been difficult to interpret, but presentation of only the best lag for the gases leaves some uncertainty as to the potential bias resulting from this approach. Results at successive lags are likely to be highly correlated, and which lag appears to be best may be influenced substantially by random variation in the data. This is a matter of concern throughout the analysis of possible lags, but especially in the two-pollutant models where results for PM and gaseous metrics are presented with different lags.

Sensitivity Analyses

One approach to enhancing confidence in observational findings is to perform sensitivity analyses. The purpose of such analyses is to determine whether the findings change when different types of analyses are performed. We have more confidence in findings that are not sensitive to different analytic approaches. Examples of such sensitivity analyses carried out by the investigators in this study include presentation of estimated effects (1) at several lags and with average lags, (2) for each of the monitoring sites, (3) with inclusion of gaseous pollutants in the models for PM, and, as noted earlier, (4) for the hospitalization data, from analyses stratified by single or multiple hospitalizations. We are not given information to determine how sensitive the findings might be to various model specifications. Nevertheless, the analysts must make decisions as appropriate choices, given that no "correct" choices can be identified. The choices made by these investigators, choices based on plausibility and model fit, seem to be as good as possible. We must be open, however, to the possibility that these choices could have influenced the reported findings.

The effect of basing estimates of exposure on different monitoring sites was explored for TSP. Although some variability in effects is present as expected, the findings do not seem to very sensitive to monitoring site.

The two-pollutant models address the sensitivity of estimated PM effects to inclusion of gaseous pollutants, one at a time. The investigators selected the best lag day to reflect the effect of the copollutants. Although this could be viewed as an approach that provides the highest likelihood of the copollutants being confounders of the PM effects, use of the average day lags for this purpose might have been preferable because they are potentially less affected by sampling variability. The PM effects for 1985–1990 for the most part were stable with inclusion of the gaseous pollutants in the models, with a few exceptions (for example, O_3 reduced the effect considerably for respiratory mortality). The PM effects for 1992–1994 were stable for some outcomes, but not for others.

Other sensitivity analyses could also have been useful. For example, given the seasonal variation in population exposures to air pollutants and in air pollution sources, especially for O_3, and some uncertainty due to seasonal adjustment, a seasonally stratified analysis would be appropriate. While stratification could incur problems of multiple testing, it would have been reassuring to see some of the important findings explored further in seasonally stratified analyses. Also, given the variable day-of-the-week effects apparent in the hospitalization series for some outcomes, sensitivity of the model to inclusion of holidays, another potential confounding factor, would have been useful.

Aerometric Data and Measurement Error

Some of the aerometric data used in this study were obtained from the AIRS database maintained by the EPA. A computer-based repository of information about airborne pollution in the United States and various countries, AIRS contains information on air quality, emissions, compliance, and enforcement. The operation of the monitoring equipment, the collection and review of data, and the assembly of the air quality database are the responsibility of state and local environmental personnel in concert with the EPA. The air pollution data are collected using standard reference methods established by the EPA. Air monitoring networks were changed in 1987 to measure PM_{10}, replacing the earlier TSP monitors.

The AIRS database was designed for the primary purpose of monitoring compliance with NAAQS regulations, and has some limitations that affect its use in health research. Air pollution levels measured at a particular monitoring site may not be representative of the population exposure for the county or urban area the monitor represents because the locations of these sites were not chosen primarily for studying the health effects of air pollution. Nonetheless, the AIRS ambient data are used as a surrogate for human exposure. Exposure estimates from these data are not likely to precisely reflect the population average for personal exposure in a particular location,

which raises the issue of exposure measurement error and its potential effect on the results.

In epidemiologic studies, errors in measuring, quantifying, or classifying exposure can affect estimates of the association between exposure and health outcomes (Zeger et al 2000). Exposure measurement error includes not only any errors resulting from the measurement instrument, but also the error in assigning individual exposures based on data from instruments some distance away from each individual. The difference between the average personal exposure, which is not measured at all in this study, and the true ambient level, which is estimated in this study but with some degree of error, may be a source of serious bias in the reported effect estimates. For the current study, such measurement error is likely to increase the noise in the data set; ie, measurement error is likely to increase the difficulty of finding and interpreting differences in effect (relative risk) across the different PM metrics because the greater imprecision in the relative risks can mask any true relative ranking of different PM metrics, should such ranking exist.

The investigators approached the question of measurement error by a separate analysis looking at the effect of monitoring site on relative risk of mortality. Their finding, that choice of monitoring site did not affect the overall results reported for TSP, indicates that data from any one monitor might be representative of ambient air pollution in the area studied. However, although this analysis is informative, it cannot answer the question of whether population exposure is reflected by ambient air monitors.

Geography

This study examines and reports results countywide. It remains possible that some health effects are geographically spotty as a result of short-scale gradients in either pollutant or population characteristics. Further work would be necessary to determine what health outcomes, if any, are concentrated in areas downwind from major sources (such as industries or roadways) or in areas heavily populated by certain possibly sensitive ethnic groups or groups in certain occupations. If such gradients occur, important but geographically limited effects will be diluted and perhaps even undetectable in countywide results.

Sulfur Artifact

Ambient SO_2 reacts with the TSP glass-fiber filters used in PM samplers to form extra SO_4^{2-}. This erroneous, or artifactual, formation of SO_4^{2-} adds to the measurement error. The investigators used PM metrics with sampling error due to artifactual formation of SO_4^{2-} (TSP– SO_4^{2-}) and without this sampling error (SO_4^{2-}). Although neither measure of acidity was found to be a useful predictor of human health outcomes, error due to sulfur artifact could have obscured a potential human health–acidity relationship.

Factor Analysis

The results from factor analysis (Figures 2 and 9) are intriguing, but were not clearly discussed or explained and are difficult to interpret from the information available. The authors present the results for factor analysis for the 1985–1990 and 1992–1994 data. On the y-axis, each figure shows PM metrics and other measures (eg meteorologic variables). The x-axis represents the factors. Inside the figures, the bars represent the amount of correlation (positive or negative) of the original variables with the resulting factors. However, the actual numerical values of the correlations (loadings) are not included in the figures, which makes comparison across factors difficult. One of the more interesting results is that $PM_{10-2.5}$ seems to be a separate factor from other PM metrics, especially given the effect estimates of $PM_{10-2.5}$ with pneumonia hospital admissions (lag 1; RR = 1.114, 95% CI: 1.006, 1.233; Appendix D) and ischemic heart disease hospital admissions (lag 2; RR = 1.101, 95% CI: 1.026, 1.181; Appendix D).

SUMMARY AND CONCLUSIONS

The authors used models with one and two pollutants to compare the effects of several PM metrics and several gases on mortality and morbidity. They found different strengths of association between specific pollutants and health outcomes; however, there was not enough separation between estimates to clearly support one relative ranking over another. The authors' finding of stronger effects for one metric over another was based on a comparison of best lag results. The lag identified as best was chosen after the fact and based on the size of the estimated relative risk. Despite using the best lag, most point estimates were similar, and the confidence bands overlapped. In order to determine the relative effects of several risk factors on a health outcome, ideally all variables under consideration would be included in a single model. However, when all air pollutants are included in a single model, the interpretation of results is difficult because the air pollutants are highly correlated.

Further difficulties in assessing health effects of particles of different sizes arise from the way PM is currently measured and classified. By definition, each of the larger PM indices contains elements of the smaller indices; therefore, it is difficult to distinguish by mass among the relative effects of PM metrics. For this study,

$PM_{2.5}$ accounted for, on average, 60% of PM_{10} mass (and up to 80% on some days); and PM_{10}, on average, accounted for 66% of TSP mass. However, the authors also assessed the effects of particles greater than 10 μm (TSP–PM_{10}) and of coarse thoracic particles ($PM_{10–2.5}$). The fact that TSP–PM_{10} was not associated with mortality in the 1985 å1990 analysis suggests that the largest particles (ie, 10 to 40 μm in diameter) were not responsible for the observed associations between TSP and mortality.

In the 1992–1994 analysis, $PM_{10–2.5}$ effect-size estimates were similar to those for $PM_{2.5}$, and sometimes even higher—for example, for ischemic heart disease and stroke. Because $PM_{10–2.5}$ and $PM_{2.5}$ were not highly correlated in correlation coefficient and factor analyses, it is possible that the observed associations between coarse particles and health outcomes were not confounded by smaller particles. This result suggests that there may still be a rationale to consider the health effects of the coarse thoracic fraction as well as the fine fraction of PM.

The investigators clearly point out that their results indicate that H^+ was not a good predictor of health outcomes. This result was not consistent with the investigators' original hypothesis that acidity plays an important role in the air pollutant–mortality relationship, and such a conclusion represents a significant shift in the investigators' paradigm regarding the role of acids in the PM mixture.

Although the current study could not definitively distinguish relative strength of effect across the PM metrics, it does provide further evidence that indicators of PM are correlated with mortality and morbidity. Whether this correlation is one of cause and effect remains a critical research question.

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